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Effect of finasteride on the sensitivity of PSA to detect prostate cancer in rebiopsy series.
Marco Oderda, Andrea Zitella, Lorenzo Richiardi, Alessandro Tizzani, Paolo Gontero

PSA supernormalisation: A surrogate of complete adenoma removal in men with benign prostatic hyperplasia.
Oreste Martella, Giuseppe Paradiso Galatioto, Gianna Pace, Carlo Vicentini

Is there a correlation between testosterone levels and the severity of the disease in male patients with obstructive sleep apnea?
Onder Canguven, Banu Salepci, Selami Albayrak, Ahmet Selimoglu, Muhsin Balaban, Mustafa Bulbul

Increased testicular 8-hydroxy-2'-deoxyguanosine (8-OHdG) and inducible nitric oxide synthetase (iNOS) and nuclear factor kappa B (NF-κB) expressions in experimental rat varicocele.
Volkan Tuğcu, Asuman Gedikbaşı, Bircan Mutlu, Ekrem Güner, Mehmet Uhri, Gülnur Andican, Emin Özbek, Ali İ. Taşçı

New perineal tensive transobturator tape (T-TOT) for postprostatectomy urinary incontinence.
Andrea Ceresoli, Davide Abed El Rahman, Alberto Cazzaniga, Gaetano Grasso Macola, Andrea Guarneri

The role of Doppler ultrasound in the diagnosis of vasculogenic impotence.
Debora Marchiori, Daniele Aloisi, Alessandro Bertaccini, Claudio Ferri, Giuseppe Martorana

Intraoperative frozen section in laparoscopic radical prostatectomy: Impact on cancer control.
Paolo Emiliozzi, Mostafà Amini, Alberto Pansadoro, Marco Martini, Vito Pansadoro

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Fibromuscular dysplasia causing renal artery aneurysm and renovascular hypertension: A case report.
Andrea Solinas, Rossano Cadoni, Massimo Usai, Mauro Frongia

Headache: A unique clinical presentation for renal cell carcinoma (RCC).
Giuseppe Candiano, Pietro Pepe, Giuseppe Grasso, Francesco Aragona

First Italian experience in single incision laparoscopic nephrectomy. Assessing and overcoming new challenges.
Stefano Gidaro, Luca Cindolo, Fabiola Raffaella Tamburro, Luigi Schips

Retrograde ejaculation and abnormal hormonal profile in a subject under treatment with valproate and phenytoin.
Jlenia Elia, Norina Imbrogno, Michele Delfino, Fernando Mazzilli

Alfuzosin induced thrombocytopenia after treatment for benign prostatic hyperplasia.
Şebnem Güner, Bircan Mutlu, Ekrem Güner, Ali İhsan Taşçı

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Francesco Rocco, Luigi Alberto Cozzi, Franco Gadda, Gabriele Cozzi, Serena Maruccia, Isabella Oliva, Elisabetta Finkelberg

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Contents

Effect of finasteride on the sensitivity of PSA to detect prostate cancer in rebiopsy series. *Pag. 135*
Marco Oderda, Andrea Zitella, Lorenzo Richiardi, Alessandro Tizzani, Paolo Gontero

PSA supernormalisation: A surrogate of complete adenoma removal in men with benign prostatic hyperplasia. *Pag. 139*
Oreste Martella, Giuseppe Paradiso Galatioto, Gianna Pace, Carlo Vicentini

Is there a correlation between testosterone levels and the severity of the disease in male patients with obstructive sleep apnea? *Pag. 143*
Onder Canguven, Banu Salepci, Selami Albayrak, Ahmet Selimoglu, Muhsin Balaban, Mustafa Bulbul

Increased testicular 8-hydroxy-2'-deoxyguanosine (8-OHdG) and inducible nitric oxide synthetase (iNOS) and nuclear factor kappa B (NF-κB) expressions in experimental rat varicocele. *Pag. 148*
Volkan Tuğcu, Asuman Gedikbaşı, Bircan Mutlu, Ekrem Güner, Mehmet Uhri, Gülnur Andican, Emin Özbek, Ali İ. Taşçı

New perineal tensive transobturator tape (T-TOT) for postprostatectomy urinary incontinence. *Pag. 154*
Andrea Ceresoli, Davide Abed El Rahman, Alberto Cazzaniga, Gaetano Grasso Macola, Andrea Guarneri

The role of Doppler ultrasound in the diagnosis of vasculogenic impotence. *Pag. 159*
Debora Marchiori, Daniele Aloisi, Alessandro Bertaccini, Claudio Ferri, Giuseppe Martorana

Intraoperative frozen section in laparoscopic radical prostatectomy: Impact on cancer control. *Pag. 164*
Paolo Emiliozzi, Mostafà Amini, Alberto Pansadoro, Marco Martini, Vito Pansadoro

Orthotopic neo- bladder in women. *Pag. 170*
Manlio Schettini

The use of the hyperbaric oxygenation therapy in urology. *Pag. 173*
Giandomenico Passavanti

Cerebellar pathology and micturitional disorders: Anatomotopographic and functional correlations. *Pag. 177*
Tiziano Zago, Umberto Pea, Gian Luca Fumagalli, Leonardo Areta, Giuliano Marzorati, Filippo Bianchi

Fibromuscular dysplasia causing renal artery aneurysm and renovascular hypertension: A case report. *Pag. 181*
Andrea Solinas, Rossano Cadoni, Massimo Usai, Mauro Frongia

Headache: A unique clinical presentation for renal cell carcinoma (RCC). *Pag. 184*
Giuseppe Candiano, Pietro Pepe, Giuseppe Grasso, Francesco Aragona

First Italian experience in single incision laparoscopic nephrectomy. Assessing and overcoming new challenges. *Pag. 187*
Stefano Gidaro, Luca Cindolo, Fabiola Raffaella Tamburro, Luigi Schips

Retrograde ejaculation and abnormal hormonal profile in a subject under treatment with valproate and phenytoin. *Pag. 193*
Jlenia Elia, Norina Imbrogno, Michele Delfino, Fernando Mazzilli

Alfuzosin induced thrombocytopenia after treatment for benign prostatic hyperplasia. *Pag. 195*
Şebnem Güner, Bircan Mutlu, Ekrem Güner, Ali İhsan Taşçı

Open intervascular nephron-sparing surgery for pyelocaliceal transitional cell carcinoma in solitary kidney planned with contrast-enhanced multidetector CT. *Pag. 198*
Francesco Rocco, Luigi Alberto Cozzi, Franco Gadda, Gabriele Cozzi, Serena Maruccia, Isabella Oliva, Elisabetta Finkelberg

Proceedings
17th National Congress SIEUN *Pag. 203*
4-6 November 2010 - Bari

ORIGINAL PAPER

Effect of finasteride on the sensitivity of PSA to detect prostate cancer in rebiopsy series.

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Summary

Objectives: *To evaluate, in a prospective study, the diagnostic accuracy of PSA in patients with a prior negative prostate biopsy who were given finasteride for 6 months.*
Materials and methods: *91 men with prior negative biopsy findings, including HGPIN and excluding ASAP, were instructed to take finasteride for 6 months. All patients were evaluated at study onset and after 6 months by clinical examination, digital rectal examination (DRE), International Prostate Symptom Score (IPSS) and National Institutes of Health Chronic Prostatitis Symptom Index (NHI-CPSI). Prostate biopsy was repeated at 6 months. PSA levels were measured at baseline and after 1, 3 and 6 months. We calculated the receiver operating characteristics (ROC) curve of PSA under the effect of finasteride for detecting prostate cancer.*
Results: *The median PSA level decreased similarly both in those with prostate cancer and in those without findings of cancer. There was no statistically significant difference between the two groups. The areas under the ROC curve (AUC) of PSA at study onset and after 6 months of therapy with finasteride were, respectively, 0.48 (95% CI 0.36-0.61) and 0.54 (95% CI 0.42-0.66). There was no statistically significant difference between the two areas.*
Conclusions: *The results of our study show that PSA itself has a low diagnostic accuracy for detecting prostate cancer in men with prior negative prostate biopsy findings. Finasteride does not seem to improve the accuracy of PSA in this particular population of patients.*

KEY WORDS: *Prostate biopsy; Finasteride; Prostate neoplasm; PSA; ROC*

Submitted 2 April 2010; Accepted 30 April 2010

INTRODUCTION

Prostate cancer is one of the most common malignancies in the world: in 2002 the number of estimated new cases was 679.000 and the number of estimated cancer-specific deaths was 221.000 (1). Diagnosis of prostate cancer can be suspected by means of increased levels of prostate-specific antigen (PSA) or abnormal findings on digital rectal examination (DRE), both of which have a low positive and negative predictive values (2). The main diagnostic tool is prostate biopsy., Recent studies have shown that even extended 10-core biopsy has dangerously high false negative rates of 10% to 34% (3), while the high number of true negatives suggests that probably many prostate biopsies performed would be unnecessary. Therefore, it would be very useful to find a new marker, with better accuracy compared to PSA only, in order to spare cancer-free patients an unnecessary biopsy and select those at higher risk of harbouring prostate cancer. This is especially true for patients with persistently elevated or rising PSA level despite prior negative biopsy findings, who continue to represent a challenging diagnostic and management dilemma for urologists (4).
Recent analysis on patients enrolled in the Prostate Cancer Prevention Trial (PCPT) suggested that finasteride, a selective inhibitor of type 2 5-alpha-reductase which converts testosterone into dihydrotestosterone, may improve the performance of PSA screening on general population and may be helpful for determining the need for a repeat biopsy in men with a previously negative PSA measure-prompted biopsy (5). It has been hypothesized that finasteride treatment would cause the greatest fall in PSA level in men with benign conditions such as benign prostatic hyperplasia, whereas men with persistently elevated PSA levels despite finasteride action, would have a higher risk of prostate cancer. Aim of the present study is to prospectively determine the diagnostic accuracy of PSA in high-risk patients with

prior negative prostate biopsy findings, who were given finasteride for 6 months, in order to assess the role of finasteride in the diagnosis of prostate cancer in a challenging population of patients, different from the one enrolled in PCPT.

Material and methods

This was an open-label, prospective study to determine the diagnostic accuracy of PSA in a different population from the one considered in PCPT, composed of patients with one prior negative prostate biopsy findings who were treated with finasteride 5 mg daily for 6 months. The study received institutional board approval. Male patients < 80 yr of age with a good performance status, who had previously undergone prostate biopsy without detecting prostate cancer were enrolled. We included patients with histological findings of high-grade prostatic intraepithelial neoplasia (HGPIN), while we excluded those with atypical small acinar proliferations (ASAP). Previous or current treatment with 5-alpha-reductase inhibitors, such as finasteride or dutasteride, constituted exclusion criteria. The patients were enrolled in the study when they received the results of the histological examination.

The serum PSA was measured at baseline and after 1, 3 and 6 months. All patients were evaluated at study onset and after 6 months by clinical examination, digital rectal exploration (DRE), International Prostate Symptom Score (IPSS) and National Institutes of Health Chronic Prostatitis Symptom Index (NHI-CPSI) (6). Treatment had to be started as soon as the histological finding of the first biopsy was available. Prostate biopsy was repeated after the 6 months treatment phase with a minimum of 12 cores taken.

The main endpoints were to calculate the ROC curves of PSA, with corresponding 95% confidence intervals, for detection of prostate cancer at the 6-month biopsy for PSA levels at baseline, PSA levels at 6 months and PSA halving during the 6-month follow-up, separately (7). We also compared the descent kinetics of PSA in the group of patients in study to the results of the prostate rebiopsy. Secondary endpoints were the incidence of prostate cancer, HGPIN and ASAP in patients with no PSA descent and the rate of incidental side effects of the finasteride treatment. Statistical analysis was performed using STATA software. The sample size was admittedly limited: the study had an 80% power to detect an AUC of at least 0.75 (alpha: 0.05). The sample size was however sufficient to obtain meaningful qualitative conclusions (8).

End of study symptoms scores for IPSS and NHI-CPSI were both analyzed for statistically significant differences from baseline with paired samples T-test.

Results

91 patients matched all criteria and were enrolled. The mean age was 68 years (sd: 6.41; age was missing for 5 patients) and the mean PSA level was 7.48 ng/ml (95% CI 6.06-8.89). All the 91 patients had prior histologic findings negative for prostate cancer; 39 of these (43%) had diagnosis of HGPIN. Seventy patients completed the study with the rebiopsy; 14 completed the study but refused final re-biopsy due to loss of confidence in this procedure or achievement of PSA values within the normality range (PSA < 4 ng/ml) while 7 were lost to follow-up. Of the 70 patients, 13 were diagnosed with prostate adenocarcinoma; the complete results are shown in Table 1.

The median PSA level decreased similarly both in those with prostate cancer and in those without findings of cancer (Figure 1). There was no statistically significant difference between the two groups (Mann-Whitney test: p = 0.86 at baseline, p = 0.39 at 1 month, p = 0.74 at 3

Table 1.

Results of the study.

Patients who underwent end of study biopsy	70
Mean basal PSA	7.89 (95% CI 6.07-9.71)
Median basal PSA	6.63 (range: 0.6-65)
Mean PSA after 1 month of therapy with finasteride	5.78 (95% CI 4.42-7.13)
Median PSA after 1 month of therapy with finasteride	4.44 (range 0.48-22)
Mean PSA after 3 months of therapy with finasteride	4.33 (95% CI 3.40-5.25)
Median PSA after 3 months of therapy with finasteride	3.23 (range: 0.3-28)
Mean PSA after 6 months of therapy with finasteride	4.26 (95% CI 3.38-5.13)
Median PSA after 6 months of therapy with finasteride	3.36 (range: 0.22-26.5)
Patients who reached PSA halving	32 (46%)
Results of the rebiopsy	
Normal prostatic parenchyma and/or chronic phlogosis and/or athrophy	35 (50%)
HGPIN	12 (17%)
ASAP	10 (14%)
Prostatic adenocarcinoma	13 (19%)
- Gleason Score 6	8
- Gleason Score 7	3
- Gleason Score 8	2
Patients without prostate cancer that reached PSA halving	24/32 (75%)
Patients with prostate cancer that reached PSA halving	8/32 (25%)
Patients without prostate cancer that did not reach PSA halving	33/38 (87%)
Patients with prostate cancer that did not reach PSA halving	5/38 (13%)

Figure 1.

Median PSA: basal and at 1, 3 e 6 months.

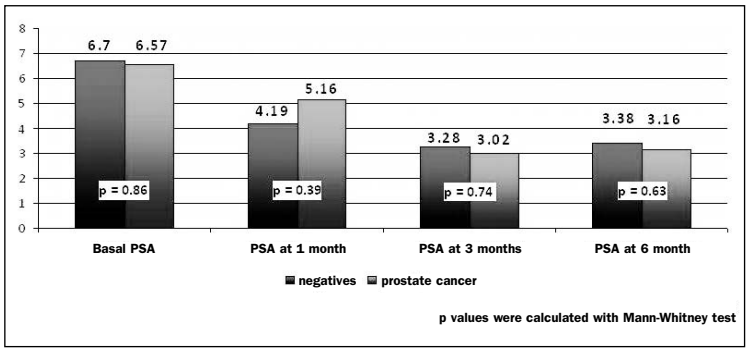


Figure 2.

Prostate cancer detection rate based on PSA halving.

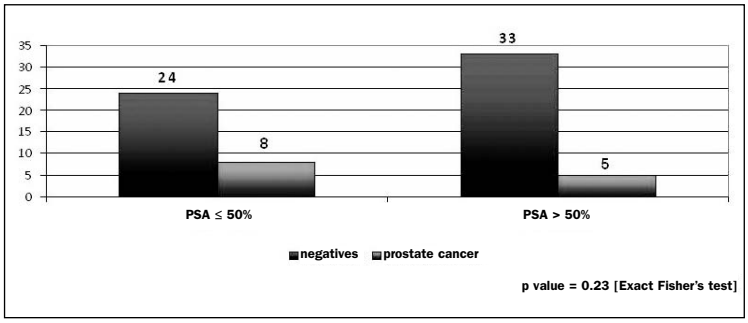
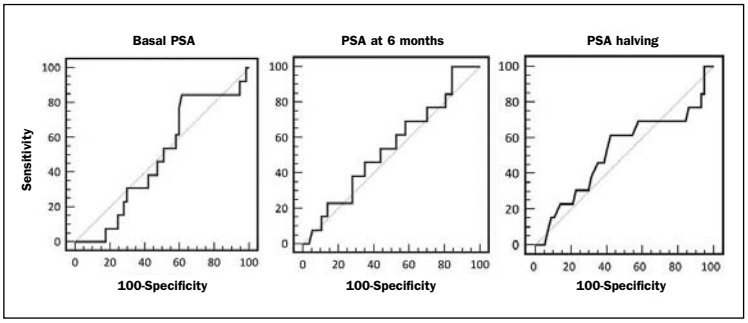


Figure 3.



months, p = 0.63 at 6 months). The detection rate of prostate cancer was not influenced by the trend of PSA decrease nor by the rate of patients with a 50% PSA reduction (Exact Fisher's test: p = 0.23) (Figure 2). The areas under ROC curve (AUCs) of PSA at study onset and after 6 months of therapy with finasteride were, respectively, 0.48 (95% CI 0.32-0.65) and 0.46 (95% CI 0.28-0.63) (Figure 3). The AUC of the PSA halving was 0.53 (95% CI 0.40-0.61) (figure 3). The IPSS and NHI-CPSI questionnaires were administered in order to evaluate the presence of urinary symptoms possibly linked to BPH (benign prostatic hyperplasia) or prostatitis, well-known causes of PSA elevation, and their variation during the finasteride treatment. Mean baseline NHI-CPSI scores were 0.95, 0.85 and 0.77 respectively for the categories pain, symptoms and quality of life, with no patient matching the diagnosis of prostatitis. Mean baseline total IPSS score was 4.71, while the IPSS score for quality of life was 0.59. Only a few patients had moderate (8-19) and severe (20-35) lower urinary tract symptoms. End of study symptoms scores for both NHI-CPSI and IPSS did not significantly differ from baseline (p > 0.05 based on paired samples T-test).

Discussion

What is the correct management of a patient with persistently high or even rising PSA level, who already underwent multiple prostate biopsies without detecting any trace of prostate cancer? This is a challenging dilemma for urologists to cope with. Such patients often seek the advice of the urologist, wanting to know the reason of their abnormal PSA level. They are worried about the possibility of harbouring prostate cancer and, on the other hand, they fear the idea of repeating another biopsy, which is surely a source of discomfort and anxiety. Nowadays, however, the risk of a prostate biopsy not detecting a tumour is still too high to let the physician ignore abnormal clinical findings. Recent studies have shown that 10 to 20% of patients with negative prostatic biopsy results will be diagnosed with prostate cancer on repeat biopsy (9). On the other hand, most biopsies performed give negative results (10), meaning that at least a part of them is likely to be unnecessary. Furthermore, another valid question still without a definite answer is when to stop the "*biopsy cascade*" in a patient that underwent multiple biopsies.

A marker more accurate than PSA would certainly help to identify high-risk patients worthy of repeating the biopsy, while sparing the cancer-free patients an unnecessary invasive procedure. According to recent analysis on patients enrolled in the PCPT, finasteride would increase the sensitivity of PSA and DRE for detection of prostate cancer and, especially in the case of PSA, significantly increased sensitivity for detection of high-grade disease (5, 11, 12). A statistical analysis performed on the PCPT population showed that the area under the receiver operating characteristic curve (AUC) of PSA for detecting prostate cancer was significantly greater for the finasteride group (0.76) than the placebo group (0.68) (5), meaning that PSA had statistically significantly better sensitivity and AUC for detecting prostate cancer in the finasteride arm of the PCPT than in the placebo arm.

In our study, we considered a completely different population from the one described in PCPT (12), trying to focus on patients with persistent diagnostic suspect, who would benefit more from the use of a marker more accurate than PSA only. Results from our series show that the diagnostic performance of PSA after finasteride is poor: the AUC of PSA for detecting prostate cancer, after six months of therapy with finasteride, was only 0.46. The area under curve is equal to 0.5 only when the variable in study cannot dis-

tinguish between the two groups: therefore, according to our data, finasteride cannot enhance the ability of PSA to distinguish between patients who have prostate cancer or not, in rebiopsy series.
Furthermore, according to our data, PSA itself has a low diagnostic accuracy for detecting prostate cancer in men with prior negative prostate biopsy findings, as shown by the AUC of basal PSA in our group in study, which was 0.48. We also evaluated the kinetics of PSA under the effect of finasteride, hypothesizing that the PSA would not halve in patients with prostate cancer. However, PSA level behaved similarly both in those with prostate cancer and in those without findings of cancer and the tumour detection rate, based on the evaluation of the PSA halving, did not improve. These findings are in contrast with the results obtained by Kaplan, who suggested that the magnitude of change in serum PSA after treatment with finasteride may be a useful adjunct in diagnosing prostate cancer in patients who have elevated serum PSA levels and previously negative prostate biopsies (13). The AUC of PSA halving for the detection of prostate cancer was only 0.52, confirming the low diagnostic power of PSA in our population. What was the likely reason for the elevated PSA in patients from our series with a negative second biopsy? Based on the internationally validated NHI-CPSI questionnaire no patients reported a symptoms score threshold consistent with the diagnosis of prostatitis either at baseline or at end of study. We can only speculate BPH as the most likely reason accounting for the high PSA levels. Data on baseline prostate volume may have strengthened our thought.
Should patients with a previous negative biopsy and a persistently elevated PSA be treated with finasteride? In our series PSA fell below 4 ng/ml, currently set as the upper normality threshold in our laboratory, in 71% of patients: this may have had positive implications on quality of life by lowering the distress related to the high PSA. On the other hand, up to 15% of our study patients refused to undergo the end of study biopsy due to the achievement of a normal PSA level. This raises potential ethical issues related to the failure to diagnose prostate cancer in a population that is currently considered at high risk for the disease.
The safety and efficacy of long term finasteride treatment to reduce the incidence of prostate cancer in the PCPT was assessed on a different study population of patient with normal baseline PSA and negative digital rectal examination (5) thus considered at low risk of prostate cancer. To our knowledge there are no published data supporting the use of finasteride in patients matching our inclusion criteria. Several other limitations have to be accounted in our study, such as the small sample size and the absence of a control group. These should be taken into account for future studies to confirm our findings.

Conclusions

In conclusion, the results of our study show that PSA itself has a low diagnostic accuracy for detecting prostate cancer in men with prior negative prostate biopsy findings. Finasteride does not improve the accuracy of PSA in this population of patients, who remain a challenging diagnostic and management dilemma.

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PSA supernormalisation: A surrogate of complete adenoma removal in men with benign prostatic hyperplasia.

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Summary

It is known that serum prostate-specific antigen levels (PSA) decrease gradually following surgery for benign prostatic hyperplasia (BPH), but there is not an established cut-off value for normal PSA after relief of obstruction. We evaluated the impact of prostatic adenoma enucleation on PSA levels in 110 patients who underwent transvesical suprapubic adenomectomy for symptomatic BPH.

We examined PSA levels before and after open surgery and weight of the prostatic adenoma as measured by the pathologist. Forty-eight percent of the patients had a preoperative PSA level between 0 and 4, 29% between 4 and 7, and 23% between 7 and 10 ng/ml. In patients with suspected abnormality on digital rectal examination or PSA > 4.0 ng/mL systematic multisite biopsies were performed preoperatively to rule out prostate cancer. The mean weight of enucleated adenoma was 87 gr (range 50-201). The mean serum PSA decreased from 4.8 ng/ml preoperatively to 0.5 ng/ml postoperatively. The mean decrease in PSA was 90% (range 70-99%). PSA was resetted at lower level in all patients irrespectively of baseline PSA levels or BPH weight. The transvesical suprapubic adenomectomy supernormalises serum PSA lower than 1 ng/ml in 96% of patients. 100% of patients have a postoperative PSA value < 1.5 ng/ml. PSA supernormalisation represents an objective measure of complete adenoma removal. The urologists should be aware of this resetted level and they should take account of it when different ablative therapies for BPH are confronted.

KEY WORDS: *Open prostatectomy; Long-term outcomes; PSA.*

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INTRODUCTION

The benign prostatic hyperplasia (BPH) is one of the most common diseases in ageing men and the lengthening of life will always require more treatments. It is known that serum prostate-specific antigen (PSA) levels gradually decrease following surgery for benign prostatic hyperplasia, but there is not an established cut-off value for normal PSA after relief of obstruction.

The aim of this study was to evaluate the impact of the enucleation of prostatic adenoma on PSA levels in men who underwent transvesical suprapubic adenomectomy for symptomatic obstructive BPH. Our attempt is to contribute to clarifying some of important aspects concerning patient follow-up.

PATIENTS AND METHODOS

Between January 2002 and July 2009, 110 men underwent transvesical suprapubic adenomectomy for the treatment of bladder outlet obstruction in our Urology Department. All patients failed conservative treatment options (α-blockers, 5 α-reductase-inhibitors or combination therapy) and were referred for surgery. Of the 110 patients, 53 (48%) had a serum PSA level less than 4 ng/ml (group 1); the other 57 (52%) had a PSA level between 4 and 10 ng/ml (group 2). In 11 patients of group 1 with suspected abnormality on digital rectal examination and in all patients of group 2 transrectal multisite biopsies from the peripheral-zone (8-12 cores) were performed before open-surgery; the biopsy samples showed no histologic evidence of prostate cancer. In 110 BPH patients, we considered the following data: preoperative PSA, postoperative PSA, BPH weight as measured by the pathologist. PSA was recorded within 1 week before surgery and 3 months postoperatively, according to an internal protocol, without any prostatic manipulation. PSA data were obtained from patients which had

their blood samples examined in our hospital laboratory (Hybritech method). For patients with an indwelling catheter were considered PSA values from blood samples taken at least 1 month before urinary retention. In those patients who received finasteride or dutasteride as prior therapy preoperative PSA was calculated by doubling the PSA measured value. Means, median, Spearman correlation coefficients, and percent change were then calculated for all variables and intervals. The Kruskall-Wallis test was used to test the significance of the difference of the change in PSA level by different PSA intervals and different BPH weights.

Results

Fortyeight percent of the patients had a preoperative PSA level between 0 and 4 ng/ml (53 pts), 29% between 4 and 7 ng/ml (32 pts), and 23% between 7 and 10 ng/ml (25 pts).

Average prostate adenoma volume measured by the pathologist was 87 gr, average pre-operative serum PSA was 4.8 ng/ml, and average post-operative PSA was 0.5 ng/ml (Table 1).

The operation determined a reduction of serum PSA of about 90%. Serum PSA levels decreased in all patients. Such reduction is always present, drastic, and in a range between 70 to 99%, irrespectively of baseline PSA levels or BPH weight. In fact when we stratified the results according to PSA or prostate weight value ranges, the differences in percentage of reduction among categories were not significant (Table 2). The transvesical suprapubic adenomectomy supernormalises the PSA lower than 1 ng/ml in 96% of patients; 100% of patients have a postoperative PSA value < 1.5 ng/ml. We evaluated the Spearman correlation between preoperative serum PSA and BPH weight confirming a statistically correlation between BPH weight and total serum PSA (R = 0.28, p = 0.02). Removal of 1 gram of BPH tissue reduced serum PSA levels by an average of 0.09 ng/mL.

Table 1.
Descriptive characteristics of study population.

Variables: 110 patients	
Mean age ± SD (yr) (range)	68 ± 13.42 (59-83)
Mean ± SD BPH weight (gr) (range)	87.1 ± 25.7 (50-201)
Mean ± SD Pre-op PSA (ng/ml) (range)	4.8 ± 2.92 (0.8-10.1)
Mean ± SD Post-op PSA (ng/ml) (range)	0.5 ± 0.62 (0.1-1.5)
PSA reduction (%) (range)	90 (70-99)
PSA reduction (ng/ml/gr) (range)	0.09 (0.01-0.17)
Spearman correlation PSA/BPH (p)	0.28 (0.02)

Table 2.
Change in PSA value after transvesical suprapubic adenomectomy in 110 patients, according to different PSA categories and BPH weight.

PSA Categories	**PSA 0-4 (n = 53)**	**PSA 4-7 (n = 32)**	**PSA 7-10 (n = 25)**
Preoperative PSA (mean ± sd)	**2.2 ± 0.8**	**5.4 ± 0.9**	9.1± 1.4
Postoperative PSA (mean ± sd)	**0.2 ± 0.3**	**0.5 ± 0.6**	1.1 ± 0.4
Reduction ng/ml	**2**	**4.9**	8
%Reduction*	**91%**	**89%**	88%
BPH Weight Categories	**Weight 50-80 gr. (n = 48)**	**Weight 80-120 gr. (n = 50)**	**Weight > 120 gr. (n = 12)**
Preoperative PSA (mean ± sd)	3.1 ± 0.8	4.9 ± 0.9	8.1 ± 1.2
Postoperative PSA (mean ± sd)	0.3 ± 0.4	0.4 ± 0.5	0.9 ± 0.6
Reduction ng/ml	2.8	4.5	7.2
%Reduction**	90%	92%	89%

* Differences in percentage of reduction among PSA categories were not significant: **Kruskall-Wallis Test: p: 0.22**

** Differences in percentage of PSA reduction among transition zone (TZ) weight categories were not significant: **Kruskall-Wallis Test: p: 0.34**

Discussion and conclusions

PSA is a prostate epithelial cell marker whose role in the diagnosis and follow-up of patients with BPH has continuously evolved (1). Expected changes in PSA with radical prostatectomy are well established (2-4). However, PSA changes in the context of open or transurethral procedures for treatment of benign disease have been less rigorously studied and most reports are quite dated. It is known that serum prostate-specific antigen levels following BPH surgery decrease gradually and reach stable values within 3-6 months, but there is not an established cut-off value for normal PSA after relief of obstruction (6-14).

The urologist's armamentarium for treating lower urinary tract symptoms that are suggestive of bladder outlet obstruction (BOO) has been expanded drastically within the last decade. The primary goal of BPH therapy must be an effective relief of symptoms associated with BOO, however, the issue of durability is an important concern when evaluating new surgical procedures for BPH.

Transurethral resection of the prostate (TURP) and other minimally invasive therapies (ablative and non-ablative) are the most common surgical procedures used to treat symptomatic obstructive BPH today.

TURP is still considered as the standard surgical treatment for symptomatic BPH, although some may argue the use of TURP in larger prostate glands; many of the new minimally invasive therapy options are characterized by the absence of long-term efficacy. Among all therapeutic choices available for treatment of BOO due to large prostate gland, open prostatectomy provides the highest probability in symptomatic improvement and the lowest failure rate (15). It is the "*true gold standard*" of BPH surgery with respect to outcome and durability (15). Open prostatectomy is characterized by a low rate of treatment failures and surgical reintervention (15-18). However, open prostatectomy has also the highest perioperative morbility, is still considered invasive and is currently performed in a minority of patients suffering from BPH with a large prostatic adenoma. These disadvantages led to the development of techniques that deliver the same results but with less morbility.

The high symptomatic improvement and the lower failure rate of open prostatectomy is due to the complete adenoma removal with anatomic enucleation; this excision, in absence of prostate cancer, causes a rapid and precipitous decline in PSA levels. This occurs because the treatment affects basically the transition zone (TZ) of the prostate, which produces more PSA per gram of tissue. We showed that 90% of serum PSA levels comes from prostatic adenoma, clearly confirming the leading role of TZ in the control of PSA levels.

Helfand et al. reported in a contemporary series of 56 patients who underwent open prostatectomy for BPH a PSA value stabilized to less than 1 ng/ml after surgery (5). *Marks et al*. reported also a average prostate specific antigen before and after open prostatectomy respectively of 4.5 ng/ml and 0.5 ng/ml (8). In 96 historically proven BPH patients *Reker et al.* reported a decline of PSA value from median 3.4 to 0.9 ng/ml after TURP (9). *Aus et al.* reported (generically) that after a complete TUR-P the PSA level should be expected to be within the normal reference range (< 4 ng/ml) (10). Finally *Wolff et al.* in a retrospective analysis of patients who developed prostate adenocarcinoma after TURP for BPH noted that these patients stabilized their PSA levels above 2.0 ng/mL (11); thus, they proposed that patients with either PSA > 2.0 ng/mL or an early rise in PSA following TURP should be checked for prostate cancer (11).

PSA is a valuable tool in the follow-up of these patients, but we need to optimise it application.

In the present study, PSA was resetted at lower level (mean PSA: 0.5 ng/ml) in all patients (96% pts PSA < 1 ng/ml; 4% pts PSA < 1.5 ng/ml). PSA supernormalisation after open prostatectomy (PSA < 1 ng/ml) is obtained by removal of the entire transition zone of the prostate. Moreover, we speculate that the changes of PSA levels would be accounted when traditional surgical therapies or minimally invasive procedures including laser techniques, are confronted, especially in large prostatic adenomas and/or in iperplastic glands with high PSA levels. PSA supernormalisation may be considered like a surrogate measure of a similarly wide open prostatic cavity (surrogate of volume); examining the change in PSA before and after intervention, it provides an objective measure of the completeness of adenoma resection. Therefore, PSA levels before and after intervention should be annexed to prostates size, symptoms score, voiding parameters and urodynamic data when evaluating surgical procedures in BPH patients.

Moreover this study properly demonstrated there is a similar percentage of reduction (90%) in post-operative PSA when we considered either entire range of PSA (0-10 ng/ml), or stratified PSA values (0-4, 4-7, 7-10 ng/ml) and/or stratified categories of BPH weight (50-80gr, 80-120, > 120 gr). Whether normal, borderline or grossly elevated before operation, serum PSA decreased to low level in all patients after removal of the obstructing adenoma. However, since peripheral zone remains following adenoma enucleation, levels do not attain the nadir associated with radical prostatectomy. The urologists should be aware of this resetted level. The reduction in PSA corresponds well with the amount of adenoma removed (r = 0.28 in our series): incomplete resection of the adenoma or occulte prostate malignancy could be the cause of failure to attain such a profound nadir in some patients. So recognition of this change is also important for the long-term screening of prostate cancer after relief of obstruction.

In conclusion PSA supernormalisation represents an objective measurement of complete adenoma removal and would be accounted when different ablative therapies for BPH are compared. To our knowledge long-term detailed outcomes using this clinical tool (PSA) have never been evaluated in prospective randomized controlled trials after surgical treatments for BPH.

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ORIGINAL PAPER

Is there a correlation between testosterone levels and the severity of the disease in male patients with obstructive sleep apnea?

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Summary

Objectives: *Obstructive sleep apnea (OSA) is a prevalent disease that can decrease quality of life. The aim of this study was to investigate the relationship between serum testosterone levels and the severity of the disease in patients with OSA.*

Material and Methods: *Severity of OSA was quantified with apnea-hypopnea index (AHI) which was defined as the total number of apneas and hypopneas per hour of sleep. Thirty-six male patients with mild-to-severe stable OSA and thirty age-matched subjects without OSA were included in this study. Erectile function was assessed by the International Index of Erectile Function (IIEF)-5. The association between severity of OSA and selected co-morbidities was evaluated and compared with findings reported in the literature.*

Results: *Mean serum testosterone levels of OSA and control patients were 462.8 ± 160.3 ng/dL and 486.9 ± 163.2 ng/dL, respectively ($p > 0.05$). There was a significant negative correlation between serum testosterone levels and AHI in patients with OSA ($r = - 0,502$, $p < 0.01$). Mean IIEF scores of OSA and control patients were 17.5 ± 5.9 and 17.4 ± 4.7, respectively ($p > 0.05$). Body mass index (BMI) of the OSA patients and control group were as 30.1 ± 0.8 and 26.9 ± 0.4, respectively ($p < 0.01$).*

Conclusions: *Serum testosterone levels were negatively correlated with BMI and the severity of OSA. Measuring testosterone level may be an additional helpful indicator in diagnosis of severity and in follow-up of OSA.*

KEY WORDS: *Erectile dysfunction; Obstructive sleep apnea; Penile erection; Questionnaires; Risk factors.*

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INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by multiple cessations of respirations during sleep responsible for intermittent hypoxia and disturbed sleep (1). The prevalence of OSA is approximately 3 to 5% for middle-aged men (2-5). Disease prevalence is higher in different population subsets, including overweight or obese people, and older individuals (2, 4). Increasingly, OSA is being recognized as an independent risk factor for several clinical consequences, including systemic hypertension, cardiovascular disease, stroke, and abnormal glucose metabolism (6, 7).

The aim of this study was to investigate the relationship between serum testosterone levels and the severity of OSA, which based on apnea-hypopnea index (AHI).

MATERIALS AND METHODS

All patients were examined between November 2008 and July 2009 at the outpatient clinics of chest diseases and urology. The study population consisted of men presenting to the clinic of chest diseases for initial evaluation with symptoms consistent with OSA as defined by specialists in sleep disorders. Patients who had sought prior evaluation for ED from a physician were excluded. No patient was using any medication for sleep disorders or erection aid at enrollment and questionnaire completion. Patients presenting with the following conditions were also excluded from this study: cardiovascular diseases, such as hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg), peripheral vascular disease, diabetes mellitus or neuro-

logical disorders. The control group was composed of 30 men with simple snoring and AHI less than 5 on polysomnogram.

All subjects volunteered to participate in this study and gave informed consent after the objectives and method of the study had been explained. All subjects were married, and they all expressed to have only one sexual partner. International Index of Erectile Function (IIEF)-5 questionnaire was used to assess erectile function and the patients were stratified by domain scores of 22-25 (no ED), 17-21 (mild ED), 12-16 (mild to moderate ED), 8-11 (moderate ED) and ≤ 8 (severe ED) (8).

We used a 12-channel polysomnograph (Sleep Screen, Viasys Healthcare, Hoechberg, Germany) and standard gold electrodes and sensors. Electroencephalography electrodes were applied at C3/A2, C4/A1, and two electrooculography electrodes were applied at the sides of both eyes to record horizontal and vertical eye movements. Submental electromyography electrodes were applied at the submentalis muscles, and electromyograms of both anterior tibialis muscles were used to analyze limb movements during sleep. Strain gauges were used to record chest and abdominal respiratory movements, and nasal pressure canulas were used to record airflow. Arterial oxygen saturation was measured using pulse oximeters applied to the index finger. On the basis of criteria established by Rechtschaffen and Kales (9), we scored every 30-second epoch of the nocturnal polysomnogram. Apnea was defined as the complete cessation of airflow for at least 10 second, whereas hypopnea was defined as a substantial reduction in airflow (> 50%) for at least 10 second or a moderate reduction in airflow (>30%) for at least 10 second with electroencephalographic arousal or oxygen desaturation (≥ 4%).

Severity of OSA was assessed by the AHI and defined as the total number of apneas and hypopneas per hour of sleep (10). Patients were divided into three groups according to AHI as mild (AHI = 5-15), moderate (AHI = 16-30), and severe (AHI= > 30).

SPSS version 11.5 (Chicago, IL, USA) was used for the statistical analysis. Continuous variables were analyzed using Student's t-test if the data were normally distributed. Otherwise, the Mann Whitney U-test was used. We analyzed the relationships between OSA scores and IIEF-5 scores by the Pearson's correlation test. A p value of < 0.05 was considered to be statistically significant.

Results

Sixty-six male subjects with active sexual life were enrolled in the study. Mean ages of OSA patients and control group were 49.5 ± 9.2 (30-67) and 47.9 ± 13.1 (26-70) years, respectively (Table 1). Thirty-six patients had abnormal (AHI ≥ 5) OSA scores. AHI was found as 43.5 ± 32.4 and 3.7 ± 0.2 in OSA patients and control group, respectively (p < 0.01). The mean duration of sleep problems was 2.7 ± 1.5 years.

Mean serum testosterone levels of OSA patients and control group were 462.8 ± 160.3 ng/dL and 486.9 ± 163.2 ng/dL, respectively (p > 0.05). Serum testosterone level was in hypogonadic level (< 310 ng/dL) in six (16.7%) and three (20%) patients in OSA and control group, respectively. There was a significant negative correlation between serum testosterone levels and AHI in patients with OSA (r = -0,502; p < 0.01) (Figure 1). Mean serum luteinizing hormone (LH) levels of OSA patients and control group were 3.73 ± 1.69 mIU/mL and 4.94 ± 2.50 mIU/mL, respectively (p < 0.05). Significant negative correlation was also observed between serum LH levels and AHI in patients with OSA (r = -0.333; p < 0.05).

Body mass index (BMI) of the OSA patients and control group were as 30.1 ± 0.8 and 26.9 ± 0.4, respectively (r = -0,414; p < 0.01) (Figure 2). There was no significant difference between men with normal and abnormal OSA score for the IIEF-5. The mean total IIEF-5 score was 17.4 ± 4.7 for those with normal OSA score and 17.5 ± 5.9 for those with abnormal OSA score (p > 0.05).

The baseline risk factor profile of the entire study group included cigarette smoking (46.9%) and hyperlipidemia (27.2%). No statistically significant difference was found

Table 1.
Comparison of baseline variables between the OSA and non-OSA groups.

	OSA (AHI ≥ 5) n = 36		Non-OSA (AHI < 5) n = 30		P-value
	mean ± SD	range	mean ± SD	range	
Age (years)	49.5 ± 9.2	30-67	47.9 ± 13.1	26-70	0.58
AHI (event per hour)	43.5 ± 32.4	6.1-121.1	3.7 ± 0.2	2.1-4.9	**< 0.01**
BMI (kg/m^2)	30.1 ± 0.8	22.2-44.1	26.9 ± 0.4	22.3-32.3	**0.01**
IIEF-5 (score)	17.5 ± 5.9	2-24	17.4 ± 4.7	6-24	0.92
LH (mIU/mL)	3.73 ± 1.69	1.47-8.02	4.94 ± 2.50	1.18-10.82	**0.02**
Testosterone (ng/dL)	462.8 ± 160.3	169-865	486.9 ± 163.2	204-845	0.54
Hyperlipidemia (n, %)	10 (27.7)		8 (26.6)		0.87
Smoking (n, %)	15 (41.6)		16 (53.3)		0.85

AHI, Apnea-hypopnea index; BMI, Body mass index; IIEF, International Index of Erectile Function; LH, Luteinizing hormone; OSA, Obstructive sleep apnea; SD, Standard deviation.

Figure 1.

Serum testosterone levels and apnea-hypopnea index in patients with obstructive sleep apnea (r = –0,502; p < 0.01).

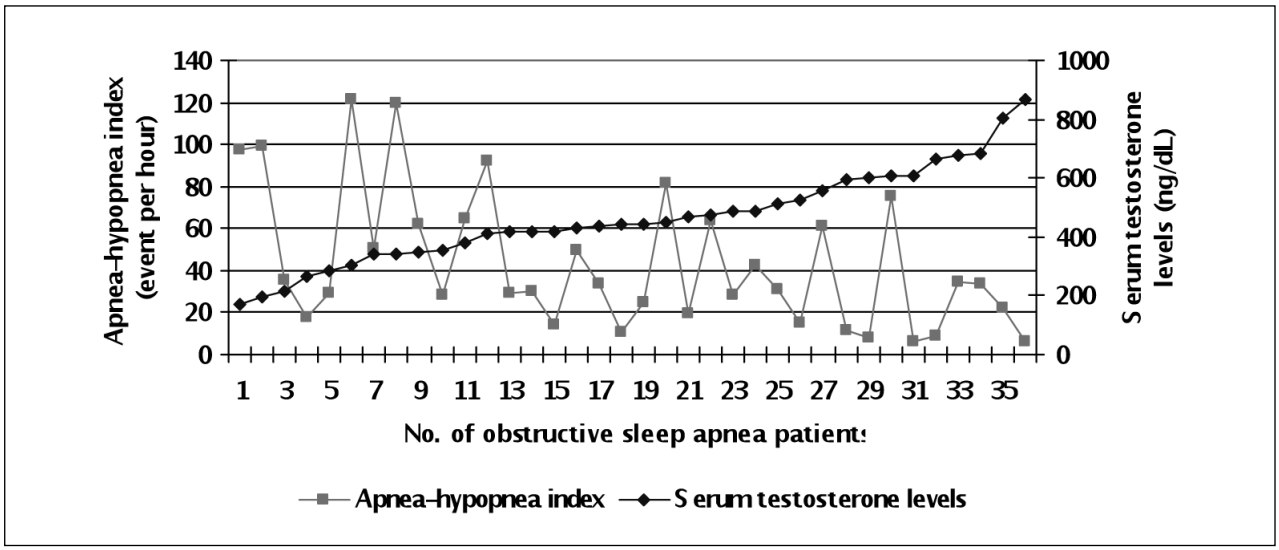
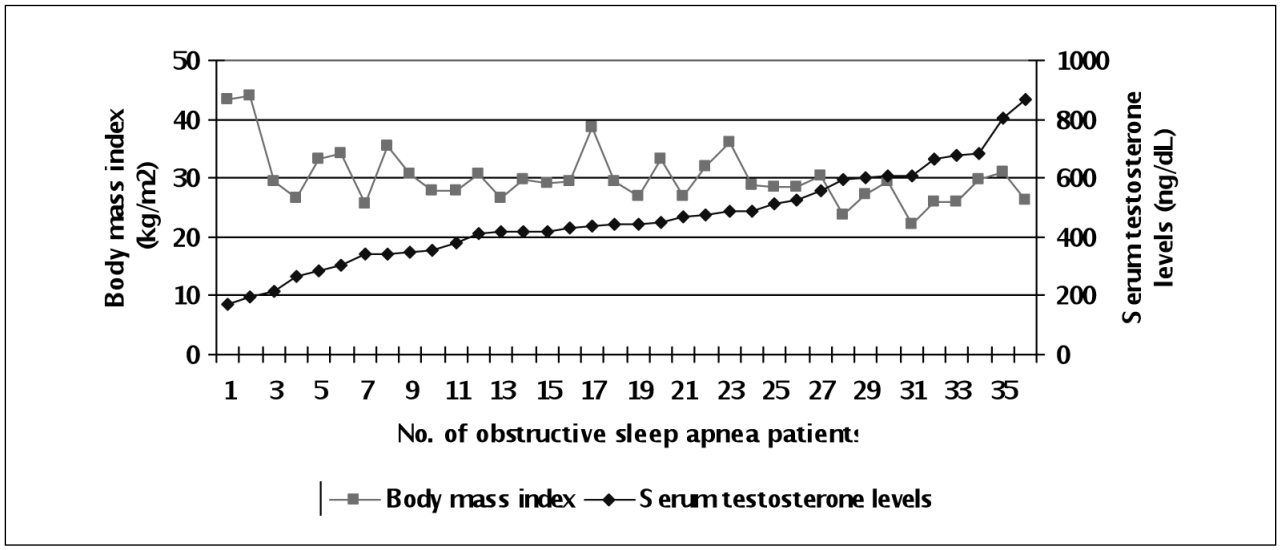


Figure 2.

Serum testosterone levels and body mass index in patients with obstructive sleep apnea (r = –0,414; p < 0.01).



in the incidence of smoking or hyperlipidemia between those with normal and those with abnormal OSA scores.

Discussion

OSA is defined as a recurrent cessation of airflow at the upper airways of no less than 10 seconds during sleep (10). In this study, we demonstrated that there was a negative correlation between testosterone and LH levels and AHI in men with OSA. The proportion of ED was similar in patients with OSA and in the control group. The IIEF-5 score was not significantly different between the OSA and control groups, which was based on AHI.

Limited numbers of clinical and laboratory studies demonstrated a relation between testosterone and abnormal sleep patterns (11-13). Decrease in sleep has been shown to lead to reduced levels of circulating androgens in healthy men and male rodents (12). In an experimental study, it was shown that sleep deprived male rats had decreased concentrations of testosterone (14).

Investigators examined the causative factors responsible for the decreased LH and testosterone secretion in middle-aged men with OSA (15). Luboshitzky and colleagues demonstrated that decrease in testosterone is mainly due to obesity and advanced age and to a lesser extent sleep fragmentation and hypoxia (15) Barrett-*Connor et al.* showed that men with lower testosterone levels had lower sleep efficiency with increased nocturnal awakenings (11). Lower testosterone levels were associated with more severe sleep-disordered breathing,

as evidenced by a higher AHI and more frequent hypoxemia (11). *Barrett-Connor et al.* explained this relation by adiposity, because low testosterone level was correlating with overweight. In a case report, it was shown that just a reduction in body weight led to improvement in respiratory function and blood oxygenation and moreover return to normal testosterone level (16).

The severity of hypoxia might be another factor in the reduction of testosterone levels, regardless of BMI (17). *Kirbas et al.* demonstrated that total testosterone levels were significantly different in between OSA and non-OSA patients (13). *Kirbas et al.* also confirmed that testosterone levels were negatively correlated with AHI and BMI (13).

In order to treat OSA and reverse testosterone levels, continuous positive airway pressure treatment (CPAP) was tried in some studies. *Grunstein et al.* applied CPAP for three months and found that CPAP treatment reversed endocrine abnormality in OSA patients (18). In another study, although the investigators applied seven-month CPAP treatment for the OSA patients, no hormonal improvement was seen (19). Although the treatment period was longer, the study population was lesser in the study of *Bratel et al.* The number of treated patients was 11 and 43 in studies of *Bratel* and *Grunstein et al.* studies, respectively (18, 19). This nearly four times difference in population number may be the explanation for why testosterone increase was not seen in *Bratel et al's* study.

Testosterone replacement therapy (TRT) is indicated for hypogonadism when there is no contraindication. In the last decade, TRT was more investigated and more frequently applied for late onset hypogonadic patients. Unfortunately, the prevalence of OSA is higher in the same age group (4). Since there are cautionary statements about TRT in OSA in literature and guidelines, most physicians avoid TRT in patients who had OSA also. In a review article, Hanafy mentioned that there is a lack of consistency in the findings connecting TRT to OSA (20). Hanafy concluded that the association between TRT and OSA is weak, since the most studies involved small numbers of men (20). Recently, *Zhuravlev et al.* treated OSA patients who had also hypogonadism with a combination of testosterone and phosphodiesterase type 5 inhibitors (PDE5-i) in addition to CPAP therapy (21). The results of the *Zhuravlev et al.* suggested positive effects of adding together testosterone and PDE5-i in hypogonadal men with OSA. Unfortunately, *Zhuravlev* and associates did not have only-testosterone treated group and the case number of the study was five, which can be accepted as relatively small (21).

The repetitive nocturnal hypoxia experienced by patients with OSA is associated with activation of a number of neuronal, humoral, thrombotic, metabolic, and inflammatory disease mechanisms, all of which have also been implicated in the pathophysiology of cardiovascular disease (1, 6, 22, 23). The impact of OSA on erectile function is of interest, because OSA introduces lack of sleep and may decrease oxygen saturation of blood.

Limited numbers of studies demonstrated a relation between OSA and male sexual disorders (24, 25). Schmidt and Wise were the first to note a relationship between OSA and ED (26). In a prevalence study, *Hirshkowitz et al.* evaluated patients with ED from point of OSA (27). *Hirshkowitz et al.* found that OSA is common in men with ED. By using IIEF questionnaire, *Teloken et al.* demonstrated that men with OSA have a significant chance of having ED (24). *Teloken* and associates showed that a correlation exists between the severity of OSA and ED. Major limitation of the *Teloken et al.'s* study was lacking of BMI and serum testosterone levels (24). There are several studies have contested this apparent relationship between OSA and ED (28, 29). Seftel and associates studied 285 men with ED (28). Although the ED patients had some sleep problems, Seftel et al found that OSA was not uniquely correlated with ED (28). *Schiavi et al.* examined 70 men, all of whom underwent polysomnography studies with evaluation of nocturnal penile tumescence, and reported no correlation between OSA and ED (29). Similarly, our study showed that men presenting with symptoms consistent with OSA did not have significant risk of ED. However, this result might have been affected by our exclusion criteria. Since we excluded patients who had sought treatment for ED, this may have influenced percentage of ED in our study.

In conclusion, the findings of this study highlighted negative correlation between testosterone and LH levels and AHI in men with OSA. The presence of OSA may decrease testosterone by itself or by metabolic syndrome (e.g. obesity, insulin resistance) associated with OSA. It is obvious that OSA have short and long-term negative effects on metabolic and hormonal milieu. We believe that monitoring testosterone level may provide additional advantage in diagnosis and determining the severity of OSA. Measuring testosterone levels, which is easier than overnight polysomnography, may also be a useful tool significantly in follow-up period of OSA patients in the future.

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ORIGINAL PAPER

Increased testicular 8-hydroxy-2'-deoxyguanosine (8-OHdG) and inducible nitric oxide synthetase (iNOS) and nuclear factor kappa B (NF-κB) expressions in experimental rat varicocele.

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Summary

Objectives: *To asses nuclear factor-κB (NF-κB), inducible NO synthase (iNOS) immunohistochemically, and 8-hydroxy-2'-deoxyguanosine (8-OHdG) biochemically, which are sensitive biological markers of oxidative damage and stress, in testes with experimental varicocele.*

Materials and Methods: *Adult rats were randomly divided into three groups. Control group (n: 10), sham group (n: 10), varicocele group (n: 10). Of 14 rats undergoing partial ligation of the left renal vein, 10 rats had developed dilation of the left spermatic vein when evaluated 3 months after varicocele-inducing surgery. The rats were sacrificed after 3 months of the varicocele-inducing surgery. Ipsilateral and contralateral testes were examined for 8-hydroxy-2'-deoxyguanosine (8-OHdG) biochemically, inducible NO synthase (iNOS) and nuclear factor-κB (NF-κB) expression immunohistochemically.*

Results: *Inducible NO synthase (iNOS), nuclear factor-κB (NF-κB) expressions and 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels in both testes of varicocele group were markedly higher compared with control and sham groups ($p < 0.01$). There was no difference between control and sham groups ($p > 0.05$).*

Conclusions: *Regarding to our results, we suggest that varicocele may produce oxidative stress in both of testes, and we believe that this stress may play a role in male fertility.*

KEY WORDS: *Varicocele; Testicular 8-OHdG; iNOS.*

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INTRODUCTION

Varicocele is a common condition in man attending infertility clinics, affecting approximately 35% to 40% of those with primary infertility and up to 80% of men with secondary infertility (1). However, pathogenesis of testicular damage or the mechanism by which varicocele produces sperm dysfunction has not been clearly identified yet (2). Deficits already identified in varicocele are scrotal/testicular hyperthermia, increased venous pressures, accumulation of toxic substances, hypoxia, hormonal imbalance and additional molecular changes (3). Studies evaluating the role of oxidative stress in male infertility have shown that infertile men with varicocele have elevated level of ROS. Several studies have shown high levels of seminal oxidative stress in men with varicocele and suggested that sperm dysfunction in men with varicocele might be partly related to oxidative stress (4). *Sokomoto et al.* reported that, those with varicocele had a significantly higher NO, HEL, and SOD activity in seminal plasma. There was a significant increase in sperm concentration and reduction in nitric oxide (NO), HEL, 8-OHdG level and SOD activity after varicocelectomy (5). The internal spermatic venous blood of patients with varicocele is characterized by venous stasis and a hypoxic condition, suggesting that increased ROS via neu-

trophil activation may be found in this venous blood. *Mitropoulos et al.* reported high oxidative stress due to the release of nitric oxide synthase and xanthine oxidase within the dilated spermatic vein (6). These authors suggested that peroxynitrite, which is formed from nitric oxide and superoxide, could be a causative factor for sperm dysfunction in patients with varicocele.

It was suggested that ROS such as hydroxyl radicals and superoxide anions act as mediators of nuclear factor κ-B (NF-κB) activation by F-κB degradation (7, 8). Excessive nitric oxide (NO) production due to elevated expression of inducible NO synthase (iNOS) might impose cytotoxic effects on kidneys (9, 10). NO at high levels can rapidly react with superoxide anion to yield potent antioxidant, peroxynitrite, which in turn causes extensive protein tyrosine nitration (11). The expression of iNOS is mainly controlled by the activation of its transcriptional factors, including NF-κB (11-13).

In varicocele bearing adolescent rats *Köksal et al.* (14) reported that iNOS was predominantly expressed in the cytoplasm of Leydig cells in each group and only a small amount of iNOS was expressed in Sertoli cells. Percentage of iNOS activity was markedly increased in the Leydig cells of varicocele bearing rats compared with control testes (15). In testicular tissue, *De Stefani et al.* reported increased NO values and the presence of other oxidant agents, representing the first sign of testicular distress (16). The formation of 8-OHdG is widely considered as a key biomarker of oxidative DNA damage (17). *Ishikawa et al.* reported that increased 8-hydroxy-2'-deoxyguanosine (8-OHdG) expression in the testis was associated with deficient spermatogenesis in infertile men with varicocele (18). The aim of the present study was to determine whether NF-κB, iNOS and 8-OHdG have a role in testicular dysfunction associated with experimental varicocele.

Materials and methods

Adult male Sprague-Dawley rats (230-250 g) were acquired from the experimental Animal Laboratory of Medical Research Center of Istanbul Faculty of Medicine (DETAM), and maintained in a 14-h light/10-h dark cycle with free access to food and water.

Varicoceles were created as previously described (19). Partial left renal vein ligation was done with the rats under intramuscular anesthesia of 5% ketamine hydrochloride (44 mg/kg). A midline incision was made to expose the left renal vein. A 4-zero silk suture was tied around the left renal vein, and a parallel 20-gauge angiocatheter was interposed at the point medial to the insertion of the adrenal and spermatic vein into the left renal vein. The ligature was placed around the left renal vein over a parallel 20-gauge angiocatheter. After placing the ligature, the angiocatheter was removed, effectively reducing the lumen of renal vein to 20 gauge. The midline incision was closed with a 3-zero silk suture. Sham-operated rats underwent a similar procedure except that no ligatures were placed. The left renal vein was dissected free but not ligated. Animals were sacrificed 3 months after creation of varicocele, and dilation of the internal spermatic veins was seen. Unoperated healthy rats served as control group. Adult rats were divided into three groups: control group (n: 10), sham group (n: 10), varicocele group (n: 10). Of 14 rats undergoing partial ligation of the left renal vein, 10 rats had developed dilation of the left spermatic vein when evaluated 3 months after varicocele-inducing surgery. The rats were sacrificed after 3 months of the varicocele-inducing surgery. Both testes were delivered into the abdomen. Rat testis were fixed in Bouin's solution. For the histopathological examination the tissues were prepared for routine examination by light microscopy, after staining with Haemotoxylin and Eosin. The slides in which there were > 30 seminiferous tubule sections were examined with a light microscope at x 200. Ipsilateral and contralateral testes were examined for 8-OHdG biochemically, iNOS and NF-κB expression immunohistochemically.

For immunohistochemical evaluation, specimens were processed for light microscopy, and sections were incubated at 60°C overnight and then dewaxed in xylene for 30 minutes. After soaking in ethanol, sections were washed with distilled water and phosphate-buffered saline (PBS) for 10 minutes. Sections were then treated with 2% trypsin in 50 mM Tris buffer (pH 7.5) at 37°C for 15 minutes and washed with PBS. Sections were delineated with a Dako pen (Dako, Glostrup, Denmark) and incubated in a solution of 3% H_2O_2 for 15 minutes to inhibit endogenous peroxidase activity. Then, sections were incubated with NF-κB/P65 (Rel A) Ab- 1 (Neomarkers R-B-1638-R7) and iNOS Ab-1 (Neomarkers R-B-1605-R7) antibodies histochemically. The Ultra-vision (Labvision) horseradish peroxidase/3-amino-9-ethylcarbazole staining protocol was used at this stage. Sections prepared for each case were examined by light microscopy by two pathologists using a double-blind study. Sections of rat lung were used as the control for immunohistochemical staining specificity, according to data provided by the antibody manufacturer.

The cases were evaluated for diffuseness and staining. According to staining diffuseness, sections were graded as follows: 0 = no staining; 1 = staining less than 25%; 2 = staining between 25% and 50%; 3 = staining between 50% and 75%; 4 = staining more than 75%. According to staining intensity, sections were graded as follows: 0 = no staining; 1 = weak but detectable above control; 2 = distinct; 3 = intense staining. Immunohistochemical values were obtained by adding diffuseness and intensity scores.

The testes were evaluated histologically with respect to the following characteristics: (i) seminiferous tubular diameters (measured with a calibrated ocular micrometer), (ii) morphology and progression of maturation of the germinal epithelium, and (iii) morphology of the tunica propria and interstitial compartments, specifically to determine whether fibrosis, hyalinization, inflammatory infiltrate and/or vascular injury could be identified. Abnormalities were graded 1 + if they were rare (confined only to isolated tubules), 2 + if they were focal (confined to a discrete field and in more than just 1 tubule), and 3 + if they were diffuse (present in all tubules uniformly) (20).

8-Hydroxy -2 deoxyguanosine (8-OHdG) amount in testis tissue was determined using NWLSS 8-OHdG ELISA Kit, a competitive enzyme linked immunosorbent assay purchased from Northwest (Vancouver, WA, Canada) following the manufacturer's instructions. It was necessary to

extract and digest sample DNA prior to assay. Testis DNA was extracted using DNasy Blood and Tissue Kit (Qiagen), Spin-Column Protocol. This protocol is designed for purification of total DNA from animal tissues. 25 mg tissue was cut up to into small pieces, and placed in a 1.5 ml microcentrifuge tube, added 180 µl Buffer ATL. Tissue samples were effectively disrupted before proteinase K digestion using a rotor-stator homogenizer. 20 µl proteinase K was added and mixed thoroughly by vortexing, than incubated at 56°C until the tissue is completely lysed (2 hour). After incubation, 4 µl RNase A (100 mg/ml) was added, mixed by vortexing, and incubated for 2 min at room temperature for RNA-free genomic DNA. Buffering conditions were adjusted to provide optimal DNA binding conditions and the lysate was loaded onto the DNeasy Mini spin column. During centrifugation, DNA was selectively bound to the DNeasy membrane as contaminants pass through. Remaining contaminants and enzyme inhibitors were removed in two efficient wash steps and DNA was then eluted in water or buffer, ready for use. Purified DNA has A260/A280 ratios of 1.7-1.9, and absorbance scans show a symmetric peak at 260 nm confirming high purity. For enzymatic digestion of DNA, extracted DNA was dissolved in buffer and added sodium acetate and 6 units of nuclease P1. DNA solution was incubated for 30 min at 37°C under Argon. After, 1M Tris-HCl buffer and 2 unit of alkaline phosphatase was added and incubated again for 30 min at 37°C under Argon. Enzymes and other macromolecules were removed by filtering through Millipore Microcon YM-10 at 14000 rpm for 10min. Samples were assayed the same day enzymatic digestion was performed. 8-OHdG levels were expressed as 8-OHdG pg/microgram DNA.

Statistical analyses of the histopathology and immunohistochemistry results among the groups was by the chi-square test, with biochemical values compared using the Mann-Whitney U-test, with $P < 0.05$ considered to indicate statistical significance.

Results

Of 14 rats undergoing partial ligation of the left renal vein, 10 rats had developed dilation of the left spermatic vein when evaluated 3 months after varicocele-inducing surgery. On microscopic examination, moderate or severe (grade 2 or 3) histopathologic changes have been observed in nine rats in varicocele group (Table 1) These changes were partial or diffuse and include arrest in spermatogenesis, focal desquamation in germinal epithelium, disorganization and degeneration of germ cells, interstitial slight fibrosis and reduction of tubular diameter.

In varicocele group, degree of histological damage was increased compared with sham and control group (Figure 1). The results of the histopathology of the left and right testis in the three groups are shown in Table 1. We found negative or slightly increased activity of p65 and iNOS in control and sham group; whereas in varicocele group activity was markedly increased. Staining of tubular cells, Leydig cells and seminiferous tubules for p65 and iNOS revealed similar positivity. p65 and iNOS activity was positive in spermatocytes and in a part of Sertoli cells (Figure 1 and 2).

We found that NF-κB activation (p65) and expression of iNOS in left and right testes of varicocele bearing rats were increased in comparison with sham and control group. Biochemically accessed amounts of 8-Hydroxy-2 deoxyguanosine in left and right testes of varicocele bearing rats was significantly high in comparison with both control and sham group ($p = 0.001$; $p < 0.01$).

Discussion

The biochemical mechanisms by which varicocele induce spermatogenic and spermatozoal dysfunction have not been completely elucidated. Researches during the last 10-15 years have implicated oxidative stress as a mediator of sperm dysfunction and may play a role in male infertility (21, 22).

Many kinds of markers can be used to evaluate oxidative stress and semen has also been examined with these markers. ROS are metabolites of NO and the generation of controlled ROS has a role in many physiological sperm functions, such as hyperactivation, capacitation and the acrosome reaction (23). ROS intermediates are also

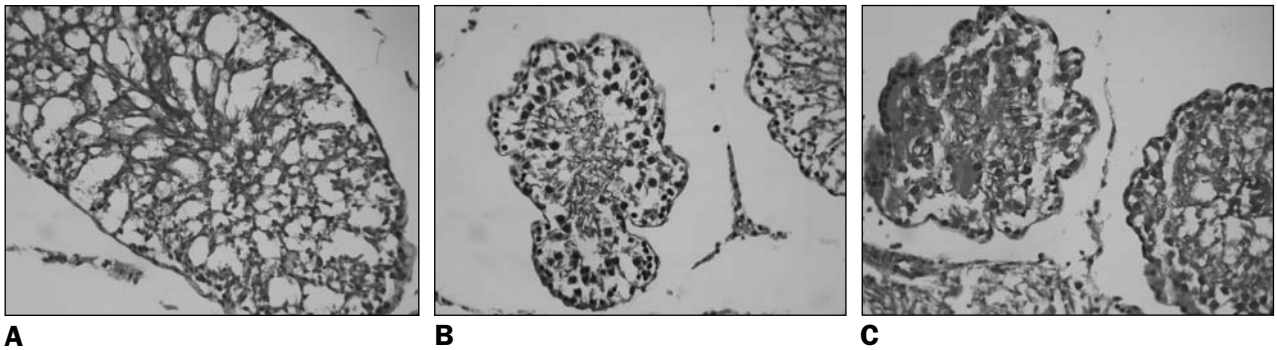
Figure 1.

H&E staining, showing:

A: Normal testis in the control, group (H&E, x 200).

B: Normal, moderate disorganization of spermatogenic activity in sham group (H&E, x 200).

C: Hipospermatogenesis, leydig cell hyperplasia, basal membrane thickening in varicocele group (H&E, x 200).



A **B** **C**

Table 1.

Degree of histological damage of both testes in each group.

	Varicocele-bearing rats (n = 10)		Sham-operated rats (n = 10)		Control rats (n = 10)	
	Right	Left	Right	Left	Right	Left
Normal histology (%)	2 (20)	2 (20)	9 (90)	8 (80)	8 (80)	9 (90)
Abnormal histology (%)						
1+	4 (40)	3 (30)	1 (10)	2 (20)	2 (20)	1 (10)
2+	3 (30)	3 (30)	-	-	-	-
3+	1 (10)	2 (20)	-	-	-	-

Values are means (SEM); 1+ = confined to isolated tubules only;
2+ = confined to discrete fields and in more than one tubule; 3+ =present in all tubules uniformly.

involved in NF-κB activation in many studies (7, 9, 10). In the present study we aimed to determine whether NF-κB, iNOS and 8-OHdG have a role in testicular dysfunction associated with experimental varicocele.

RT-PCR or Northern blotting analyses are functional assays by which the actual activity of iNOS is measured. Northern blotting provides a more quantitative way of measuring iNOS and p65 activity. Therefore, it is a limitation of this study that Northern blotting analyses have not been used.

Table 2.

Concentration of 8 OHdG (pg/µg DNA) in varicocele group.

Rat	Left	Right
1	8.286	4.425
2	6.085	7.063
3	6.592	6.100
4	6.915	8.145
5	5.881	4.642
6	6.054	4.625
7	7.287	5.442
8	8.036	6.582
9	4.071	8.371
10	7.072	4.264

Left testicle, varicocele group mean 6.754 ± 0.891.
Right testicle, varicocele group mean 5.771 ± 1.286.

Table 3.

Concentration of 8 OHdG (pg/µg DNA) in sham group.

Rat	Left	Right
1	4.983	2.477
2	4.427	2.340
3	2.208	3.642
4	4.378	4.955
5	3.372	4.260
6	1.884	2.441
7	4.373	2.347
8	2.123	1.860
9	2.452	2.120
10	2.786	2.640

Left testicle, varicocele group mean 3.079 ± 1.008.
Right testicle, varicocele group mean 2.459 ± 0.826.

Varicocele, which is the leading cause of male infertility, is associated with both increased production of NO and spermatozoal reactive oxygen species. NO can interact with ROS to form peroxynitrite, which induces protein damage by forming nitrotyrosine. It is generally thought that the endothelial NOS derived NO at low levels, regulates the physiological vasodilatation, while excess NO production due to elevated expression of iNOS can cause cytotoxic effects in surrounding cells. The contribution of NO to tissue injury can be a direct effect mediated by NO itself (24). NF-κB was suggested to mediate lipopolysaccharide and γ-interferon induction of NOS in rat alveolar macrophages (25) and murine bone marrow-derived macrophages (26), furthermore *Xie et al.* reported the presence of potential NF-κB binding sites in the 5'-flanking region of the iNOS gene (8).

Moiro K. *O'Bryan et al.* reported that iNOS is expressed constitutively in Leydig cells and in a stage-specific manner in Sertoli, peritubular and spermatogenic cells in the normal testis. Expression was increased in a dose-dependent manner in all these cell types during lipopolysaccharide (LPS)-induced inflammation (27). Furthermore, *Santoro et al.* reported that iNOS is up regulated in the testes of adolescents with left idiopathic varicocele similarly to that occurring in the rat testis after lipopolysaccharide treatment (28). In varicocele induced rats, *Türker et al.* found that percentage of iNOS activity was slightly increased in the Leydig cells of sham group compared with control group, but the difference was not significant when compared to the varicocele group. iNOS is expressed in most cells only after induction by immunologic and inflammatory stimuli (29). *Türker et al.* considers that, activation of peritoneal macrophages occurs in the operation, and because of macrophages products such as IL-1 and TNF-α might be involved in directly regulating Leydig cell function, iNOS immunoreactivity was slightly increased in the Leydig cells of sham group compared with control group. Potential sources of IL-1-like factor may be activated peritoneal macrophages in the operation (15).

Table 4.

Concentration of 8 OHdG (pg/µg DNA) in control group.

Rat	Left	Right
1	2.100	1.200
2	1.898	3.450
3	3.986	2.208
4	4.775	0.727
5	1.322	1.700
6	1.456	1.560
7	1.356	1.450
8	1.902	2.124
9	2.152	1.895
10	1.800	1.921

Left testicle, varicocele group mean 1.900 ± 0.842
Right testicle, varicocele group mean 1.798 ± 0.496.

Figure 2.

Immunohistochemical staining, showing:

A: negative iNOS staining in Leydig cells in control group (x 200).

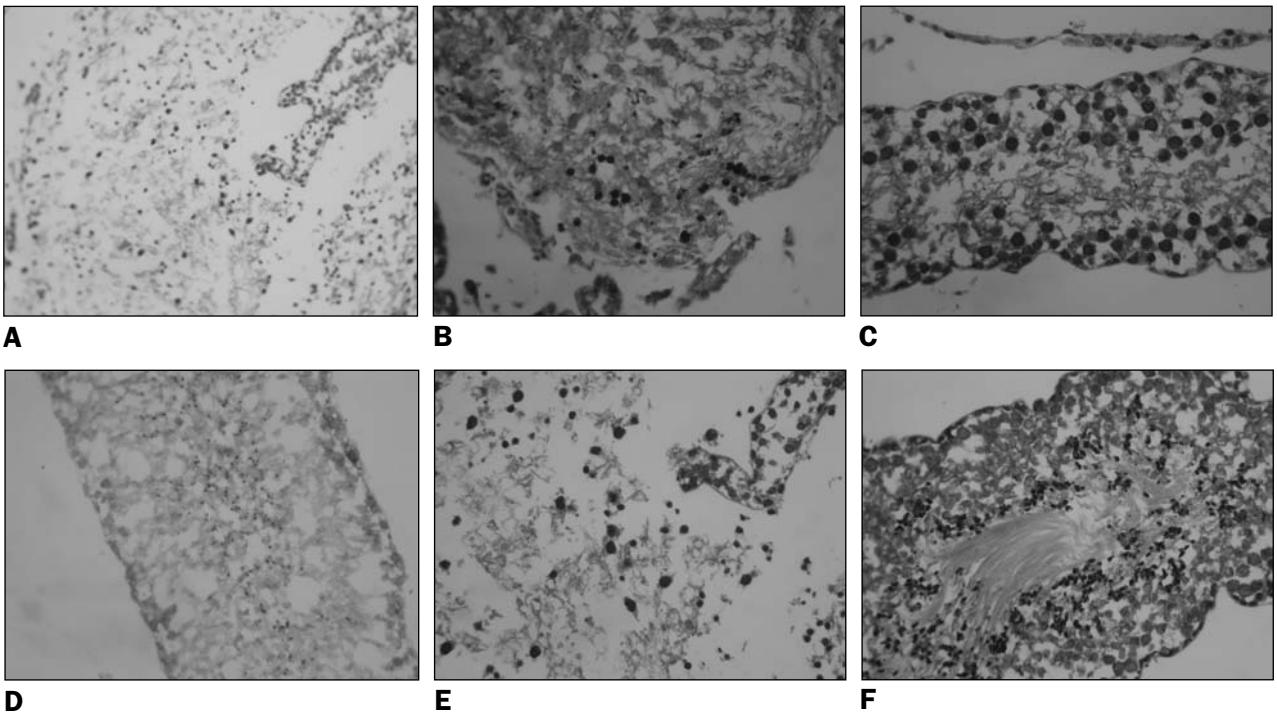
B: slightly increased iNOS activity in sham group (x 200).

C: positive iNOS staining in varicocele group (x 200).

D: NF-κB/p65 negativity of seminifer tubules in control group (x 200).

E: slightly increased NF-κB/p65 activity in seminifer tubules in sham group (x 200).

F: NF-κB/p65 positivity of seminifer tubules and Leydig cells in varicocele group (x 200).



We found negative or slightly increased activity of p65 and iNOS in control and sham group; whereas in varicocele group activity was markedly increased. These immunohistochemical results demonstrate that varicocele is related with oxidative stress.

The expression of iNOS is mainly controlled by activation of its transcriptional factors including NF-κB, *Zhang et al.* reported that homocysteine, at pathophysiological concentrations, was able to activate NF-κB, causing enhanced iNOS expression in macrophages (30).

In our previous study we have shown iNOS and p65 (NF-κB) expressions were significantly increased in nephrotoxicity induced by gentamicin (12). In present study we found that there were significant differences in iNOS and p65 expression between both testes of varicocele and control group. iNOS and p65 activity were both increased in left and right testes of varicocele group compared with control group. *Nallella et al.* noted that infertile patients with varicocele had higher interleukin-6 and ROS, and decreased total antioxidant capacity (31).

Shen et al. suggested that sperm DNA damage is closely related to male infertility and 8-OHdG is a sensitive marker of oxydative DNA damage caused by ROS in human sperm (32). Some studies have shown that the 8-OHdG level in sperm is closely associated with the presence of antioxydants in semen (5, 33, 34).

Conclusion

To our knowledge, the present is the first study to measure 8-OHdG as a marker of oxydative stress in testicular tissue.

We found that comparison of the 8-OHdG level changes in both testes of each group. There were no statistically significant differences ($p > 0, 05$) between right and left testicular tissues of each group. But there were statistically significant difference in 8-OHdG level between both testes of varicocele group in comparison with both testes of control group and sham group.

Regarding to our results, we suggest that varicocele may produce oxidative stress on the testis, and we believe that oxidative stress begins in the testis and that this stress may play a role in male fertility.

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ORIGINAL PAPER

New perineal tensive transobturator tape (T-TOT) for postprostatectomy urinary incontinence.

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Summary

Abstract: *Bulbourethral transobturator sling data from other investigators report a success rate from 53% to 85%. Since the degree of sling tension and its adjustment seems to be important for achieving complete urinary continence we present results on the first consecutive 12 patients, with mild post prostatectomy stress urinary incontinence – defined as – less than 500 ml, who underwent a new perineal tensive transobturator polypropylene tape (T-TOT) procedure at our institution.*

Results: Pre-operative mean abdominal leak point pressure (ALPP) was 23 cm H_2O (sd +/- 10), retrograde leak point pressure (RLPP) was 24 cm H_2O (sd +/- 6) and the mean pad test was 324 g (sd +/- 176). The overall success rate has been of 58.3% (7 patients) complete responders (CR), 33.3% (4 pts) partial responders (PR) and 8.33% (1 patient) failure. No significant urodynamic outlet obstruction nor urethral erosion occurred at 9-month follow up occurred. Post operative ICIQ-SF questionnaire score dropped from 11 to 3 with significant statistical evidence ($p < 0.01$).

Conclusion: perineal T-TOT showed safe and effective results similar to conventional bulbourethral transobturator male slings without obstructive symptoms despite maximal tension was used. Anyway longer prospective follow up is needed to determine the long-term efficacy of this procedure and the effective preservation from urethral erosion.

KEY WORDS: *Postprostatectomy urinary incontinence; Transobturator bulbourethral sling; Urinary continence.*

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INTRODUCTION

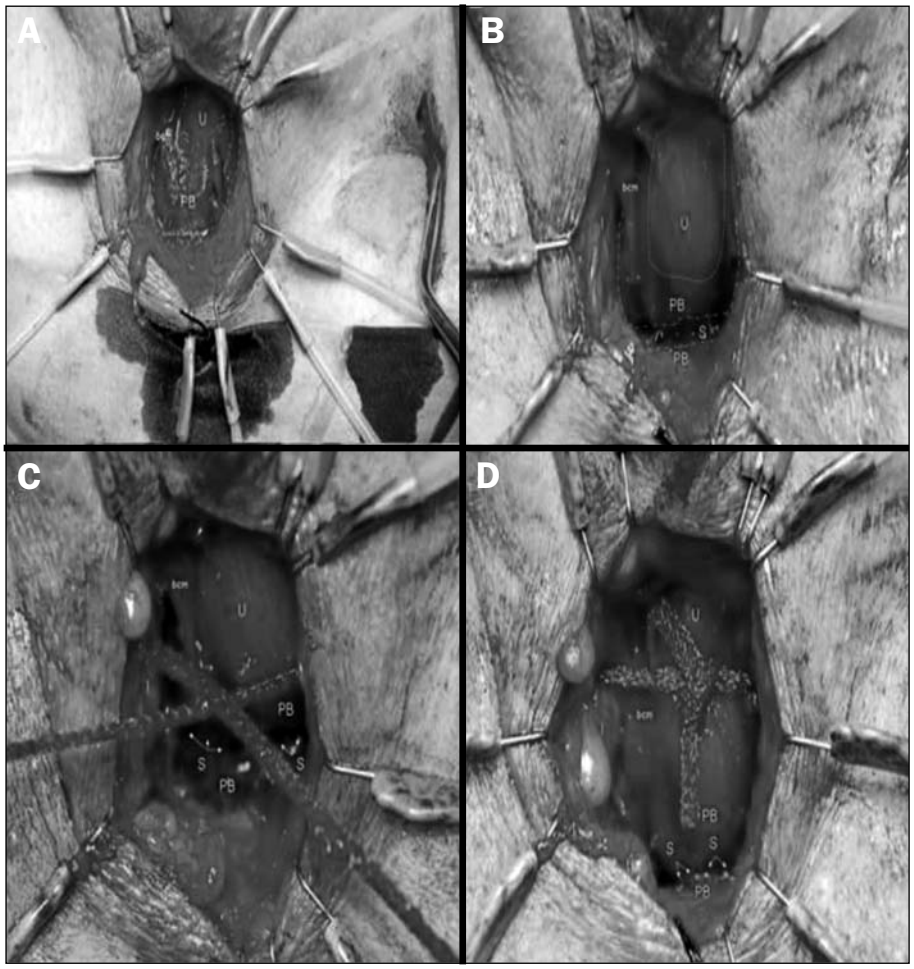
Urinary incontinence after radical prostatectomy impacts quality of life negatively (1) and ranges from 5% to 30% (2-4). Sphincter dysfunction alone or combined with detrusor functional abnormalities are recognized causes for over 96% of cases (5-10). Surgical damage to pubourethral ligaments or muscolofascial urethral support may lead to sphincter dysfunction while bladder neck demolition may lead to bladder decentralization. Prophylaxis is carried on intraoperatively at the time of the radical prostatectomy (11-14) by procedures that preserve anatomical urethral and rabdomyosphincter integrity at the prostatic apex (15), the bladder neck (11, 16), the pubprostatic ligaments (17) or the urethral rabdomyosphincter (13, 18). Postprostatectomy treatments include conservative and second-line therapy involving artficial urinary sphincter (AUS) placemement, urethral bulking agents injections, periurethral balloons and bulbourethral sling procedures.

High revision rates with the AUS and low success rates with bulking agents and periurethral balloons have prompted the development of efficient urethral sling procedures. Sling data from other investigators report a success rate from 53 to 85% (8, 19, 20) with curve of success rates stabilizing at 6 month follow up (21). Retropubic and perineal slings are based on active bulbar compression with increase of outlet resistance (8, 21-24) but may erode urethra up to 6% of cases as erosion occurres with excessive urethral pressure (25).

Transobturator tapes (TOT) are less obstructive by means of attachments to the obturator foramen preventing from sling-tension related urethral erosion (26). The tape function is based on a cranial cephalization of the urogenital diaphragm posterior to the urethra replacing its functional support lost by the time of the prostatectomy after pubourethral ligaments and/or muscolofascial plate cut. Since the degree of sling tension and its adjust-

Figure 1.

(A) Left helicoidal needle and perineal body after transobturator out-in passage. (B) Sling positioned under perineal body 2 cm posterior the bulbar urethra. (C) Distal wings of the sling after medialization into the subcutaneous space over the Colles' fascia. (D) Sling tensioned and tightened showing active tension underneath the perineal body safeaway from the urethra. U = bulbar urethra; PB = perineal body; S = polypropylene sling; bcm = bulbocavernous muscles.



ment seems to be important for achieving complete urinary continence (27) many intraoperative measurement have been used to gain the optimal one such as retrograde urethral pressure (27-29), cough test (30) or urethral resistance (24). Anyway intraoperative urethral pressure decreases in the follow up indicating a sling relaxation (20) with possibility of incontinence recurrence (27). Sling relaxation may be prevented by its maximal tension. We present results on the first consecutive 12 patients who underwent a new tensive perineal body transobturator polypropylene tape (T-TOT) procedure at our institution from March 2007 to February 2009 for mild-moderate post radical prostatectomy urinary incontinence.

Materials and methods

12 patients with stabilized moderate post radical prostatectomy underwent an original perineal body T-TOT placement at our institution. All patients reported a mean daily pad test less than 500 ml. According to the International Continence Society (31) preoperative supine 50 ml/min medium fill videourodynamics and retrograde leak point pressure test (RLPP) with static urethral pressure profile selected patients with simple sphincter deficiency (SD) or combined with decreased bladder compliance. In mild incontinence patients abdominal leak point pressure test (ALPP) may be negative despite anatomical and functional sphincter deficiency (14). For this reason it has not been considered specific for SD. Based on other studies we used for compliance the cut off value of 10 ml/cm H_2O (5, 32, 33).

Cystourethroscopy was used to rule out anastomotic or urethral stricture that should be treated and healed before sling surgery. Prospective videourodynamics and urethroscopy were evaluated in all patients, before surgery and at 9 month follow up. The signficance of the observed differences in proportions was tested by Pearsons' chi 2 and values < 0.05 were considered significant. A 30 cm x 30 cm polypropylene mesh sling has been shaped intra operatively into a sling 30 cm width and 1 cm height distally with a progressive up-to 3 cm height in the middle. Through a midline perineal incision the perineal body is isolated laterally without any bulbar urethral cephalic dissection. Ischiourethral dissection was carried on to guarantee urethral mobilization when the perineal body is cephalized by the sling. The polypropylene shaped tape has been placed beneath the perineal body 2 cm posterior to the bulbar urethra (Figure 1). Each end passed from the perineal incision into the obturator foramen bilaterally with a out-in percutaneous needle technique accordingly to Gozzi's technique (26). The medial portion of the shaped sling pushes over only the perineal body cephalating the membranous urethra toward the bladder.

Because the tape is actively acting only onto the perineal body with no direct contact to the bulbar urethra, its tightening may be maximal, without risk of urethral obstruction and erosion. Both ends of the tape are finally brought from the subcutaneous obturator tissues into the median incision by a subcutaneous course over the Colles' fascia. Once the medial supeficial perineal tissues have been sutured together to the Colles' fascia the tape's ends are

tightened together to prevent from sling slippage (26) or long term de-tensioning. A draining indwelling 18Ch Foley catheter is left and removed within 24 hours.
Questionnaire analysis. Patient's satisfaction has been assessed by means of ICIQL-SF questionnaire for incontinence (31).
Data collection and statistical analysis. Urodynamics data pertinent to outcome assessment were collected and recorded as the means, ranges and SD. Pearson's chi-square test was used to assess differences among the groups of complete responders (CR), partial responders (PR) and failure (F) using SPSS software. To detect independent predictors of outcome multivariate analysis with the logistic regression model followed by a stepwise forward procedure was done. Two tailor values of $p < 0.05$ were considered statistically significant.

Results

Average age was 72 years. No patients had previous endoscopic, surgical or radiotherapy treatment. Mean follow up was 26 months (from 24 to 27 months). Pre operative mean ALPP was 23 cm H_2O (sd +/- 10), RLPP was 24 cm H_2O (sd +/- 6) and the mean pad test was 324 g (sd +/- 176). The overall success rate has been of 58.3% (7 pts) complete responders (CR), 33.3% (4 pts) partial responders (PR) and 8.33% (1 patient) failure (F). A 10 ml/cm H_2O bladder compliance cut off, similar to the suggested from Leach (32), provided a significant predictive value of the surgical outcome (91% specifity and 75% sensibility). No difference was found in the recovery of maximum urethral pressure or/and functional urethral length after T-TOT procedure, in accord with prior investigators (14). A not statistically significant ($p > 0.05$) mean improvement of 12 cm H_2O in MUCP has been seen in CR patients while of 7 cm H_2O in PR patients. RLPP showed an increase in average from 22 (+- 6.7) to 57 (+- 6.5) cm H_20 ($p > 0.05$). Despite the considerable tension exerted on the sling no clinical significant outlet obstruction happened nor perineal pain longer than a fortnight was recorded in these series as previously experienced in literature (21).
A patient suffering from sling infection was cured conservately with parenteral wide spectrum antibiotic therapy for one week. Another patient suffered from a perineal "*butterfly*" hematoma and this was associated to transitory acute complete urinary retention. No post operative residual urine occurred nor urodynamic urethral obstruction at 26 months follow up. A patient complained a "*de novo*" overactive bladder with low grade relapse of the incontinence within 6 months from surgery. Post operative quality of life SF questionnaire mean score dropped from 11 to 3 with significant statistical evidence ($p < 0,05$).

Discussion

Sphincter deficiency is responsible of 96% of stabilized post prostatectomy incontinence with direct correlation to its degree (5, 34). Surgical cut of the pubo-urethral ligaments leads to an intraoperatory kidnap of the distal urethral stump into the urogenital diaphragm and may be followed by a postoperative certain degree of urethral or perineal descent and urinary incontinence (26). A not squared urethral section at the prostatic apex may lead either to shorter urethral functional length or direct damage to urethral sphincter with low MUCP (9, 35).
Postoperative urinary incontinence may last for 12 months stabilizing in 4% of patients as definitive. TENS and Kegel exercises make recovery faster in 80% of patients in the first 4 months without overall continence improvement (unpublished data) enhancing conservative results obtained with Kegel exercises alone (36). Nagouchi (14) and than Rocco (13) demostrated that a preventive intraoperatory anterior or posterior urethral suspension may lead to an early post operative continence status. The lack of significance in long term efficacy may suggest pubourethral ligaments integrity as a major predictive factor in post operative continence
preservation. However a posterior support may be also delivered later by cranial cephalisation of the urogenital diaphragm from a bulbar urethral transobturator sling procedure (26) with the result of an enhancement of the residual urethral rabdomyosphincter muscular action (37).
Worldwide a bulbar urethral sling procedure is worth for medium degree of incontinence. For larger amounts of incontinence secondary to complete sphincter deficiency the placement of an articial urinary sphincter (AUS) is indicated. If bulbar urethral sling procedure is performed in complete sphincter deficiency, incomplete recovery may occur. In these series patients suffered from a daily incontinence lower to 500 ml. Moreover, tape tensioning correlates in literature with clinical outcome (27) but also with urethral erosion(26), despite maximal TOT tension in cadavers showed no possibility to totally obstruct the urethra (26). Urethral erosion may be due to a too distal sling placement on the proximal urethral bulb or to its incomplete mobilization (38) or to the thining of the ventral bulbar urethra at the dissection (39). Particularly, in our opinion, when a thin urethra is posteriorly sustained by a rough sling in terms of surface rigidity. With a too distal placement of the trans obturator sling, the force is applied directly onto the urethral lumen, not onto the spongious tissue that lies inferior to the urethral lumen. This incorrect placement leads to obstruction or distortion of the urethral lumen (39). Double blinded multicentric prospective trials may be helpful in stating if smoothness of the polipropylene sling may be important as the surgical technique to avoid urethral erosion. However, in these series the anterior perineal body has been interposed between the bulbar urethra and the polipropylene sling ensuring a vascularized muscular cushion preventing from urethral erosion at maximal sling tension, showing clinical outcome similar to that provided from standard bulbourethral trans obturator male slings (26). Correlation in post operative overcome has been found only with urodynamic compliance. If over 10 ml/cm H20 patients resulted totally cured in 80% of cases. If under, only 35,2% of patients were found with CR while 5,8% improved at least.
Compliance showed to be a specific (91%) predictor of complete post operative success. Sensibility is lower (75%) perhaps because other factors may act in the continence balance of the urethral sphincteric unit. Tape fix-

ation differs from original Gozzi's technique (26). Maximal tension in these series has been provided from trans-location of the lateral wings of the tape in a subcoutaneus tunnel into the median surgical wound. Maximal tension has been sustained from the ileopubic branch of the obturator foramen, and fixation was obtained by knotting both ends of the tape together. Although placement of the sling with passage of a needle through the perineum is thought to cause symptomatic perineal nerve entrapment (24) in these series symptoms were not significant suggesting that may be due more to bone screws than to a tensive perineal nerve compression. An overall success of 91,6% (CR + PR), is strongly suggestive for clinical efficacy of this tensive sling procedure. In these series T-TOT procedure missed urodynamic statistical evidence of recovery. We may explain this missing value because urodynamics are performed in laying position by default. While tape suspension give active sustain to the urogenital diaphragm deiscensus in the standing position.

Conclusion

Perineal T-TOT showed effective results similar to conventional bulbourethral transobturator male sling in the management of post radical prostatectomy incontinent patients when daily urinary incontinence was less than 500 ml, not showing obstructive symptoms despite maximal tension was used. Anyway longer prospective follow up is needed to determine the long-term efficacy of this procedure and the effective preservation from urethral erosion.

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ORIGINAL PAPER

The role of Doppler ultrasound in the diagnosis of vasculogenic impotence.

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Summary

Objective: *Many authors have demonstrated that cardiovascular diseases (CVD) and their related risk factors can predict erectile dysfunction (ED). The penile Doppler ultrasonography is a method to evaluate the cavernous blood flow in people with suspected vasculogenic impotence. The goal of our study was to evaluate if erectile dysfunction is associated to a vascular disease and which is the role of penile Doppler investigation.*

Material and Methods: *90 patients (group 1) complaining ED, but no symptoms of CVD were prospectively evaluated with penile Doppler ultrasound. The controls (group 2) were 45 apparently healthy subjects. Both groups were submitted to carotid and aortal-iliac Doppler ultrasonography.*

Results: *50 patients (mean age 60.5 ± 4.6 years) in group 1 (IIEF < 15) and 45 subjects (mean age 59.5 ± 4.6 years) in group 2 (IIEF > 15) were recruited. Mean age, height, LDL-cholesterol and blood pressure value were not statistically different (p = 0.417) between the two groups. Statistically significant differences were found in weight values (p = 0.016). Only 8 patients (4%) were affected by arterial insufficiency and 42.1% by veno-occlusive mechanism insufficiency (p > 0.05). The cavernosal artery diameters were within 0.7 ± 0.2 and 1.2 ± 0.1 mm. All patients with a diagnosis of vasculogenic impotence of either arterial or venous origin were found asymptomatically affected by both a diffuse thickenings > 1 mm or a non hemodynamic plaque in the other vessels examined (carotid arteries or aorta or iliac arteries).*

Discussion: *Looking at our results, erectile dysfunction is associated to diffuse thickness > 1 mm or with a non hemodynamic plaque of atherosclerotic origin in other vessels. These data confirm the theory that impotence has to be considered as a risk marker for cardiovascular disease (CVD) in men with no cardiovascular symptoms. In our opinion, the penile echo Doppler is not able to show any endothelial dysfunction in terms of loss of mediator releasing.*

Conclusion: *in case of suspect vasculogenic impotence, even if penile Doppler is not pathological, it would be worth performing a systemic Doppler evaluation of main arteries in order to investigate the presence of atherosclerotic finding and institute a preventive therapy for CVD.*

KEY WORDS: *Impotence; Doppler ultrasound.*

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INTRODUCTION

It has been estimated that 150 million men worldwide are affected by erectile dysfunction (ED) with an incidence of 50% in general population aged between 40 and 70 years (1-2). Many authors have demonstrated that cardiovascular diseases and their related risk factors can predict ED. This correlation is based on the theory that a common pathogenesis exists (3). Atherosclerosis which is the main cause of vascular damage and consequently vascular disease has been demonstrated to develop as endothelial dysfunction (4). Penile tumescence and erection is achieved by local vasomotion induced by the releasing of the cyclic GMP and cyclic AMP pathways in endothelial cells the whole modulated by various chemomediators such as nitric osside (NO). Atherosclerosis, which is considered a degenerative disease, induces a damage of the endothelial function and a luminal narrowing in the whole arterial district. Hence, following the "artery size" hypothesis, the atherosclerosis is a sys-

temic disease and atherosclerotic plaque is likely to be symptomatic in arteries of a smaller diameter, such as in the penis, than in larger sized arteries (3).This is the reason why many authors report that people affected by a silent systemic vascular disease complain impotence as their first symptom. In fact, cavernous arteries have a smaller diameter than other arterial beds. The penile Doppler ultrasonography is a method to evaluate the cavernous blood flow and it is reasonably indicated in people with suspected vasculogenic impotence. In this prospective study we tried to evaluate if erectile dysfunction is associated to a silent vascular disease and the role of penile Doppler investigation in predicting a vasculogenic impotence.

Materials and methods

We prospectively evaluated 50 patients (group 1) referred to our institution who complained ED but not symptoms suggestive for cardiovascular diseases. The controls (group 2) were 45 apparently healthy subjects. All data were evaluated following the criteria of a case-controlled double blind study in which the medical vascular specialist did not know the results of the penile Doppler ultrasound and the urologist was blinded regarding the carotid and aortic-iliac vessels Doppler evaluation. Group 1 patients met the following inclusion criteria: age within 50 and 65 years old, no symptoms or evidence of cardiovascular disease and presence of erectile dysfunction assessed using the International Index of Erectile Function short form (IIEF-5). Inclusion criteria of the controls were the same as for group 1 except for not complying impotence. Patients presenting impotence associated to psychological disorders or to a pathological metabolic or hormonal profile or previously submitted to pelvic or vascular surgery or radiotherapy or pelvic trauma or presenting neurological disorders or if affected by any kind of cancer or Peyronies' disease or assuming antihypertensive drugs, antipsychotics, H2-antiistamine drugs or anti androgens, were excluded from both groups. Before being enrolled in the study all patients were interviewed for their medical history and psychological profile, and were submitted to laboratory testing. A written informed consent was provided to all patients of the two groups. All patients of group 1 were submitted to cavernosal arteries Doppler ultrasound using a linear probe (Esaote Technos MPX) with a 7.5 MHz frequency. After positioning the patient supine, the Doppler parameters peak systolic velocity (PSV), end diastolic velocity (EDV), resistant index (RI) and the diameters of both cavernosal arteries were recorded at 10 and 30 minutes after the injection of 10 microgram of prostaglandin-E into corpus cavernous (ICI) near the penile basis. Arterial insufficiency was considered in case of PSV value less than 25 cm/sec while EDV > 5 cm/sec was classified as venous insufficiency. Both groups were submitted to carotid and aortal-iliac Doppler ultrasonography. The medical vascular specialist performed the ultrasound examination of carotids with an Esaote Technos MPX linear (4-10 MHz) ultrasound scanner. The patients were evaluated in the supine position with the head elevated at 15 degrees and turned away from the ultrasound probe. The measurements of PSV, EDV, CIMT (carotid intimal-media thickness) and the luminal diameter were obtained longitudinally in the common, internal and external carotid. Diffuse CIMT or atherosclerotic plaque was evaluated. In order to reduce the abdominal swelling patients were requested to reduce the intake of fruit, beans and vegetable starting from at least three days before the abdominal examination. The abdominal aortic-iliac examination was performed with an Esaote Technos MPX with convex probe 2.5 MHz frequency. The aorta and both iliac vessels were transversally and longitudinally scanned up nearby and down to the renal ostium. PSV, EDV, the luminal diameter were obtained and the luminal diffuse thickness as well.

Results

A total of 95 patients aged between 50-65 years (mean age 60.15 ± 4.52) matched the inclusion criteria. Among these patients, 50 (mean age 60.5 ± 4.6 years) belonged to group 1 (IIEF < 15), while 45 (mean age 59.5 ± 4.6 years) to group 2 (IIEF > 15). Mean ages of the impotent and potent patients were not statistically different (p = 0.536) as much as height (p = 0.417). Statistically significant differences were found in weight values when the two groups were compared (p = 0.016). According to this statistical difference we have also correlated the LDL-cholesterol and blood pressure values of the two populations. No differences were found in physiological or pathological values when both groups were examined

Figure 1.
Degree of right carotid lumen narrowing between two groups.

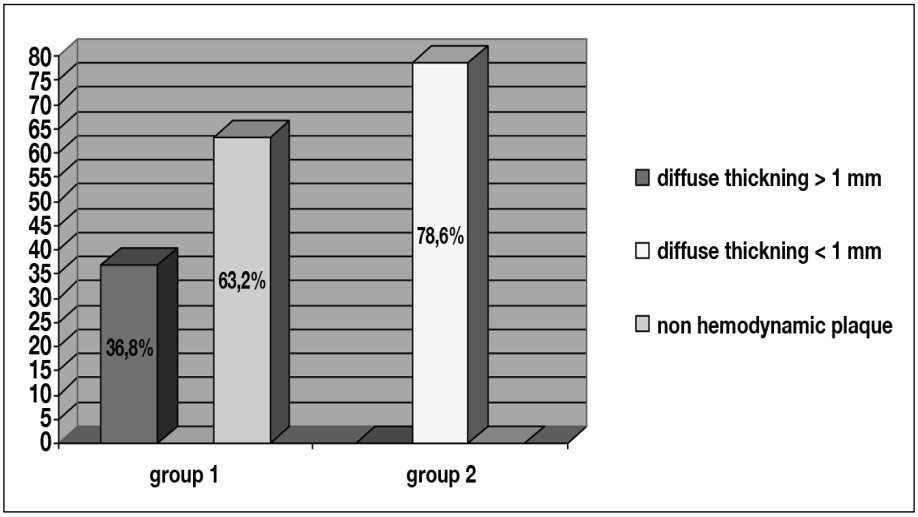
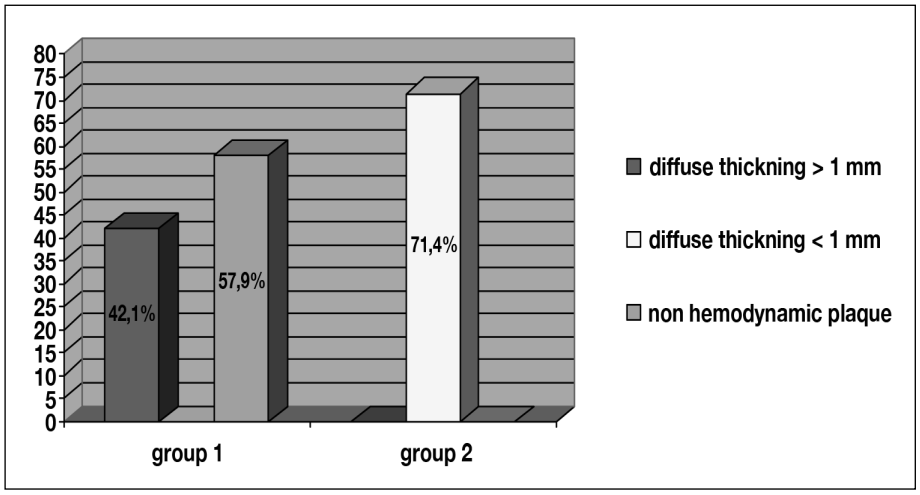


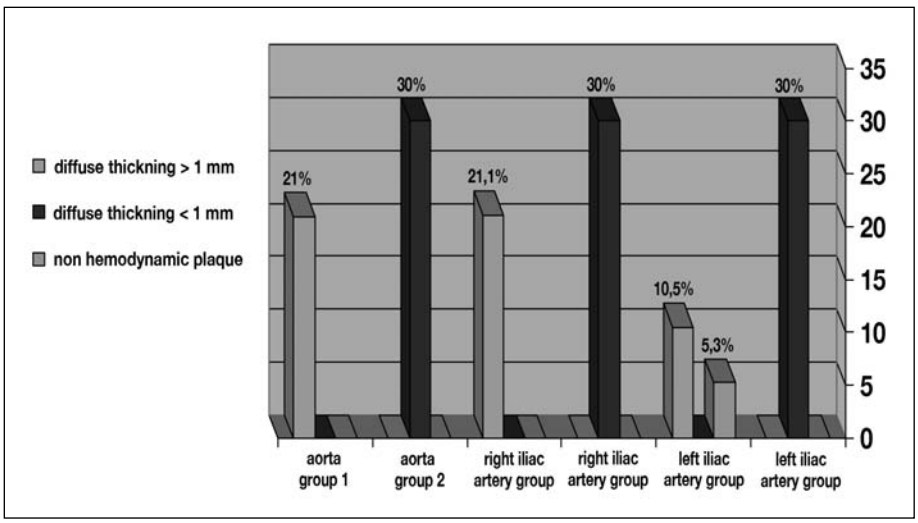
Figure 2.
Degree of left carotid lumen narrowing between two groups.



(p > 0.05). With the threshold of 25 cm/sec for PSV, EDV of < 5 cm/sec and RI < 90% the variant analysis showed that only 8 patients (4%) were affected by arterial insufficiency (1 patient monolateral and 3 patients bilateral) and 42.1% by veno-occlusive mechanism insufficiency (p > 0.05). The cavernosal artery diameters were within 0.7 ± 0.2 and 1.2 ± 0.1 mm. All patients with a diagnosis of vasculogenic impotence of either arterial or venous origin were found asymptomatically affected by both a diffuse thickenings > 1 mm or a non hemodynamic plaque in the other vessels examined (carotid arteries or aorta or iliac arteries).

All patients of the two groups have varying degrees of right carotid artery lumen narrowing defined as diffuse thickening > 1 mm (36.8% of ED) and < 1 mm (78.6% non ED) or a non hemodynamic plaques (63.2% ED) (Figure 1). All patients showed also a left carotid diffuse thickening > 1 mm (42.1% ED) and < 1 mm (71.4% non ED) or non hemodynamic plaques (57.9% ED) (Figure 2). Statistically significant differences were found in the severity of lumen narrowing in the right (p < 0.05), but not in the left carotid artery when ED and non ED patients' groups were compared. No statistical significances were found in the diffuse thickening > 1 mm or in plaques in both aorta and iliac arteries (p > 0.05). Only 21% of the ED patients showed a diffuse thickening > 1 mm in the abdominal aorta while none of the group 1 and 2 had a non hemodynamic plaque. We have found a non hemodynamic plaque or a diffuse thickening > 1 mm in the left common iliac artery in 5.3% and 10.5% of impotent patients respectively. 21.1% of group 1 also showed a diffuse thickening > 1 mm of right common iliac artery. Not one of the controls had abdominal aortic-iliac lumen narrowing but 30.2% showed a diffuse thickening < 1 mm. A statistical difference in thickness was found within the two groups (p = 0.01) (Figure 3). In the ED group, one patient with arterial insufficiency and 15 patients with veno-occlusive mechanism deficiency had a bilateral non hemodynamic carotid plaque inducing a stenosis of 14-49%. Only 2 patients with arterial insufficiency had a lonely non hemodynamic plaque localized at the right carotid artery inducing a lumen narrowing of 50-79%. Of the rest of the patients with veno-occlusive mechanism deficiency, 7 had a lonely non hemodynamic plaque localized at the right carotid artery and 13 patients at the left carotid artery. Only one with arterial insufficiency and 10 with veno-occlusive mechanism deficiency presented a diffuse carotid arteries, aortal-iliac arteries thickness > 1 mm.

Figure 3.
Degree of aorto- iliac lumen narrowing between two groups.



Discussion

The diagnosis of impotence due to arterial insufficiency or veno-occlusive mechanism deficiency can be better established by selective penile angiography or cavernography, but these techniques are more invasive and expensive than a penile color Doppler evaluation (5-6). Literature data is controversial regarding the sensibility and the specificity of the accepted available parameters such as PSV less than 25 cm/sec indicating an arterial disease and or EDV > 5 cm/sec for venous leakage or the validity of measurements taken after the intracav-

ernous injection (7-10). Looking at our results, in only the 4% of the sample the cut-off values were predictive of arterial insufficiency and 42.1% of a venous defect. In more than half of the patients complaining ED the color Doppler was not pathological and all the resting 49 impotent patients gained a rigid erection between 10 and 30 minutes after ICI of 10mcg of prostaglandin E-1. The interesting result of this study was that in all patients erectile dysfunction related directly with diffuse thickness >1mm or with a non hemodynamic plaque of atherosclerotic origin in other vessels (11-12). In fact, the diffuse thickness discovered in group 2 was < 1 mm. This data confirms the theory that impotence is has to be considered a risk marker for cardiovascular disease (CVD) in men with no cardiovascular symptoms. The basis of this relationship is the endothelial dysfunction involving all vascular district (13-15). Since Virchow, more than 150 years ago, it has been suggested that it could be the vessels abnormalities inducing a thrombosis process, further studies were taken in order to understand all the mechanisms involved in the vascular damage (16). All the findings were addressed to the integrity of the endothelial function. Until a few years ago the endothelium has been considered only a flattened cell layer on the internal elastic lamina fencing off the blood cells and components from the vascular wall, while it plays a fundamental role in the regulation of vessels tone and permeability as well as synthesis of various mediators and growth factors. The loss of these important functions may determine pathological changes (17). In atherosclerosis, a systemic chronic progressive disease, loss of endothelium function and secretory capacity are the earliest detectable physiologic manifestations. In this first long asymptomatic phase these alterations are associated to the remodelling of the vascular wall with a still flow preservation. Subsequently, the atherosclerotic plaque expands to the point at which it limits flow producing ischemia. In this condition, vasculogenic erectile dysfunction is believed to generate from the penis' abnormal vascular flow. In fact, according to the "artery size" theory, impotence is a good predictor of CVD because the diameter of penile arteries is smaller than other arterial lumens. But how can we explain that the majority of penile Doppler ultrasounds that we performed in this study did not show any anomalies of penile vascular flow suggestive of arterial insufficiency and or venous defect? Impaired endothelial function represents the initial step in developing a pathologic atherogenetic process without overt disease and in the penis is responsible for loss of vasomotion mechanism that is essential for erection. Deficiency of biochemical mediators and loss of sinusoidal architecture associated with atrophy of penile smooth muscle induces loss of compliance with consequent both difficult to fill and store blood for adequate erection (13). In our experience, a plaque or severe diffuse thickness (> 1 mm) due to atherosclerosis development, in cavernosal arteries was a very rare ultrasound finding. Therefore, the "artery size" theory is not applicable to correlate impotence to CVD. We believe that in physiological conditions, the effect of endothelial damage determines an erectile dysfunction that can be hiden by the effect of the vasoactive agent administration during the ultrasound. In our opinion, the endothelial dysfunction cannot be evaluated with the penile Doppler ultrasounds in patients with suspected vasculogenic impotence and consequently can not be excluded. In the other vessels examined where the vasomotion mechanism is not as essential as in the penis, the effect of endothelial dysfunction is symptomatic only in cases of hemodynamic stenosis. Looking at our results, we think that impairments in the penile hemodynamic of erection can be diagnosed only in the presence of the cavernosal lumen narrowing inducing alteration in blood flow or in the case of veno-occlusive mechanism deficiency (18). The penile echo Doppler is not able to show any endothelial dysfunction in terms of the loss of mediator releasing which is the first symptomatic phenomenon. So in case of a suspect of vasculogenic impotence, even if penile Doppler is not pathological, it could be worth it to perform a systemic main arterial Doppler evaluation in order to investigate the presence of atherosclerotic finding and institute a preventive therapy for CVD.

Conclusion

Even if penile Doppler ultrasound is not pathological, a vasculogenic impotence is not to be excluded and a systemic main arterial Doppler evaluation could be used to confirm the diagnostic suspect. According to these results, it appears the role of Doppler ultrasound is not investigative in cases of suspected vascular impotence when there is only the endothelial dysfunction of cavernal vessels. Many and further studies need to confirm our findings. The most important consideration is that all of these impotent patients need to be screened for asymptomatic CVD.

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ORIGINAL PAPER

Intraoperative frozen section in laparoscopic radical prostatectomy: Impact on cancer control.

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Summary

Background: *Intraoperative Frozen Section (IFS) with further tissue resection in case of positive margins has been proposed to decrease positive surgical margins rate during radical prostatectomy. There are a few reports on the benefits of this potential reduction of positive margins (PSM).*

Objective: *The aim of this study is to assess the oncological advantages of PSM rate reduction with the use of IFS and additional tissue excision in case of PSM.*

Design, setting and partecipants: *270 patients undergoing laparoscopic radical prostatectomy were included in a prospective study, to evaluate the results of further tissue excision in case of PSM at IFS. Median age was 65 yrs. Median PSA was 7.0 ng/ml.*

Intervention: *The prostate was extracted during the operation. IFS was performed in all patients on the prostate surface, at the base, the apex and along the postero-lateral aspect of the gland. In case of PSM additional tissue was excised from the site of the prostatic bed corresponding to the surgical margin.*

Measurements: *Endpoint was biochemical recurrence-free survival.*

Results and limitations: *PSM were found in 67 patients (24.8%). With additional tissue resection, PSM rate dropped from 24.8% to 12.6%. Decreased PSM after further resection didn't improve biochemical-free survival. Patients with initial PSM at IFS rendered negative with further resection, had similar results if compared to patients with margins still positive, and worse results if compared to patients with negative margins (NSM). Biochemical recurrence rate was 2.95% at 58 months in 203 patients with NSM, 15.1% at 54 months in 33 patients with PSM at IFS that were rendered negative after further resection, and 11.7% at 67 months in 34 patients with still PSM after additional resection. These results were confirmed also according to: stage, nerve-sparing procedure, Gleason score.*

Conclusions: *Our data don't support IFS during radical prostatectomy to improve biochemical-free survival..*

KEY WORDS: *Frozen Section; Positive margins; Prostate cancer; Radical prostatectomy.*

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INTRODUCTION

Frozen section (IFS) during radical prostatectomy was first introduced to evaluate intraoperatively pelvic lymph nodes, for detection of occult metastases. In 1993 (1) a French group proposed to use frozen section to assess the status of surgical margins during retropubic radical prostatectomy, in order to perform further tissue resection on the site corresponding to the positive margin.

A positive margin is, at his best definition, "*a tumor extending to the inked surface of the prostatectomy specimen that the surgeon has cut across*" (2).

Positive surgical margins are an independent prognostic factor of prostate cancer recurrence (3, 4).

Several studies have reported a significant reduction of positive surgical margins (PSM) rate with the use of frozen section and additional tissue resection, with no further tumor found in 39.7-85.7% of additional resected specimens (5-8).

Heidenreich (9) advocates that intropeative frozen section during nerve-sparing radical prostatectomy should be considered more frequently in patients with possible

extracapsular disease to preserve the neurovascular bundles, whenever oncologically indicated, to improve postoperative potency and continence, thus achieving a better quality of life.
However, the oncological implications of this decreased positive surgical margin rate are not clear. Most papers dealing with frozen section for positive margins at radical prostatectomy lack of follow-up, which is essential to assess oncological results. In a retrospective study, in 98 patients undergoing further negative tissue resection for positive surgical margins at IFS or for intraoperatively palpable lesions, *Rabbani et al.* (5) have reported a trend toward improved biochemical disease free-survival at 36 months.
The aim of this study is to investigate the assumption that a positive margin at frozen section, with no tumor found at further local resection, is oncologically equivalent to a negative surgical margin (NSM) or at least has somehow a better prognosis than a positive margin which remains positive.

Methods

From March 2001 to March 2007, 270 consecutive patients undergoing laparoscopic radical prostatectomy were enrolled in a prospective study, to evaluate the results of intraoperative frozen section and further resection in case of positive margins. Median age was 65 years (range 45-76). All patients were evaluated preoperatively with PSA, digital rectal examination, and Magnetic Resonance with Endorectal Coil. Median biopsy Gleason score was 6 (range 4-10). Median PSA was 7.0 ng/ml (range 0.49-36.2.). Bone scan was performed only when PSA was 10 ng/ml or higher, or Gleason score was > 7. A bilateral nerve-sparing procedure was performed in 113 patients. The specimen was extracted with an endobag during the operation from a short 3-4 cm midline incision, at the site of a 12 mm trocar, and analyzed with frozen section for positive surgical margins at the apex, at the base and along the postero-lateral aspect bilaterally. When a positive margin was found, further tissue was resected, corresponding to the positive site. In case of positive margin at the apex, further soft tissue and/or a ring of urethral stump was resected. In case of nerve-sparing procedure, the neuro-vascular bundle omolateral to the positive margin was resected. When the positive margin was at the base, further tissue was obtained from the bladder neck area.
No adjuvant therapy (nor radiotherapy neither hormone therapy) was performed immediately after prostatectomy. Patients were followed with PSA every 3 months and with digital rectal examination every 6 months. A PSA level of 0.20 ng/ml or greater was considered as biochemical recurrence.

Results

Frozen section was performed in all 270 patients. Median time from specimen extraction to results of frozen section was 17' (range 13'-22'). Pathological stage was pT2 in 175 (64.8%) and pT3 in 95 (35.2%) patients. Pathological Gleason Score was 4 in 2 patients (0.7%), 5 in 3 (1.1%), 6 in 108 (40%), 7 in 145 (53.7%), 8 in 6 (2.2%), and 9 in 6 patients (2.2%). A positive margin was found in 67 patients (24.8%). In these 67 patients the site of positive margin was at apex in 18 (27.3%), at postero-lateral aspect in 39 (57.6%), at base in 8 (12.1%), at seminal vesicles in 2 (3.1%). In 33 patients, no tumor was found in additional tissue resected. In 34 patients, tumor was present in further resected tissue. The results of frozen section were confirmed in all 270 cases by permanent section. No patient with negative margins at frozen section had positive margins at definitive pathology.
After frozen section and further resection, positive surgical margin rate decreased from 24.8% (67/270) to 12.6% (34/270).
In 175 patients with pT2 prostate cancer, 24 patients (13.7%) had positive surgical margins, No residual disease with further resection was found in 16 patients (9.1%). Additional resection decreased positive margin rate from 13.7% to 4.6%.
In 95 patients with pT3 prostate cancer, 43 patients (45.2%) had positive surgical margins. No residual disease with further resection was found in 14 patients (14.7%). Additional resection decreased positive margin rate from 45.2% to 30.5%.
In 113 patients undergoing a bilateral nerve-sparing procedure, 28 patients (24.7%) had positive surgical margins. No residual disease with further resection was found in 13 patients (11.4%). Additional resection decreased positive margin rate from 24.7% to 13.3%. These results are summarized in Table 1.
However, a decreased positive margin rate after further resection didn't correlate with an improvement of biochemical free-survival. Patients with negative margins after initial positive margin at frozen section and further resection had similar biochemical survival rates if compared to patients with positive margins, and worse biochemical survival rates if compared to patients with negative margins.

Table 1.

Decrease of positive margins rate after additional tissue resection.

	N	PSM (%)	PSM→NSM	FINAL PSM (%)
Overall	270	67 (24.8)	67→33	34 (12.6)
pT2	175	24 (13.7)	24→16	8 (4.6)
pT3	95	43 (45.2)	43→17	26 (27.3)
Nerve-sparing	113	28 (24.7)	28→13	15 (13.3)

Biochemical recurrence rate was 2.95% at 58 months in 203 patients with negative surgical margins, and 15.1% at 54 months in 33 patients with positive margins at frozen section that were rendered negative after further resection. Overall, patients with negative margins at further resection had biochemical recurrence rate similar to those with positive margins (15.1% vs 11.7%, P = 0.35) (Table 2).

The absence of any oncological advantage of negative margins achieved after further resection for a positive margins was confirmed in the subgroup of pT3 patients and in the subgroup of patients undergoing a nerve-sparing procedure (Table 3).

In pT2 patients, probably due to more favorable disease, a difference between patients with negative, positive rendered negative after further resection, and positive margins couldn't be found, even with a longer followup (70 months) (Table 4).

The absence of any advantage of further resection on the site of positive margins was confirmed also stratifying patients according to the presence or absence of a Gleason pattern 4.

In multivariate Cox proportional hazard analysis, independent predictors of biochemical recurrence at 5 five years were Gleason score > 6 (P = 0.019), pathological stage (T2 vs. T3) (P = 0.014), preoperative PSA (lower than

Table 2.

Disease free survival in patients with negative margins, with positive margins rendered negative, and with positive margins.

OVERALL	N	F-UP (months)	PSA recurrence (%)	P value
NSM	203	58	6 (2.95)	⌐0.0002
PSM→NSG	**33**	**54**	**5 (15.1)**	
PSM	34	67	4 (11.7)	⌙0.35

Table 3.

Disease free survival in p T3 patients with negative margins, with positive margins rendered negative, and with positive margins.

pT3	N	F-UP (months)	PSA recurrence (%)	P value
NSM	65	52	3 (4.6)	⌐0.0011
PSM→NSG	**17**	**55**	**5 (29.4)**	
PSM	26	53	5 (19.2)	⌙0.22

Table 4.

Disease free survival in p T2 patients with negative margins, with positive margins rendered negative, and with positive margins.

pT2	N	F-UP (months)	PSA recurrence (%)	P value
NSM	151	68	11 (7.2)	⌐0.279
PSM→NSG	**16**	**70**	**0**	
PSM	8	70	0	⌙NS

Table 5.

Disease free survival in patients with negative margins, with positive margins rendered negative, and with positive margins, according to Gleason score.

Gleason ≥ 7	N	F-UP (months)	PSA recurrence (%)	P value
NSM	108	59	3 (2.7)	⌐0.0263
PSM→NSG	**26**	**63**	**3 (11.5)**	
PSM	23	61	4 (17.4)	⌙0.279

Gleason < 7	N	F-UP (months)	PSA recurrence (%)	P value
NSM	95	63	2 (2.1)	⌐0.0328
PSM→NSG	**7**	**58**	**1 (14.2)**	
PSM	11	65	2 (18.1)	⌙0.414

10 ng/ml, or equal or higher than 10 ng/ml) (P = 0.01), and positive margins status (P = 0.009), no matter if negative after further resection.

Discussion

Positive margin rate is related to a higher risk of disease recurrence after radical prostatectomy (10-12).

Improved clinical assessment (13) and modifications of the surgical technique (14-16) have all been proposed to decrease PSM rate.

The literature is not standardized about the modalities and indications to intraoperative frozen section. It can be performed with two different approaches: specimen obtained from prostate surface or specimen obtained from periprostatic surgical bed biopsies after gland removal. Additional tissue is usually removed from the prostatic bed when cancer is present on the specimen, from the anatomical site corresponding to the positive margin. Intraoperative frozen section can be performed systematically or when there is the suspicion of a positive margin. Frozen section with pathological assessment of surgical margin status during retropubic radical prostatectomy was first introduced by *Ponthieu at al.* in 1993 (1). Positive margins were found in 8 of 66 (12%) pts. undergoing radical prostatectomy. In 6 cases further resection was performed, until no cancer was found at frozen section. All pts. underwent adjuvant radiotherapy. No followup was reported.

Initially intraoperative frozen section has been used to detect potential postero-lateral positive margins during procedures with preservation of neuro-vascular bundles, with the aim to perform bundle excision and to decrease positive margins rate in case of positive IFS, or to spare the neurovascular bundle in case of intraoperative palpable lesion and negative IFS. In 1999, *Cangiano et al.* (17) proposed frozen section of postero-lateral prostate margins during nerve-sparing retropubic radical prostatectomy. Of 48 pts, 9 (18%) had positive margins. The ipsilateral neuro-vascular bundle was widely excised. At 20.6 months, no patient had disease recurrence. In another retrospective study, (18) 101 pts at risk of surgical positive margins underwent nerve-sparing retropubic radical prostatectomy; intraoperative frozen section was performed on postero-lateral aspect of prostate surface. Fifteen patients had positive margins at IFS. No tumor was found in 12 patients (80%) in further resected tissue. At 33 months, prostate cancer recurred in 2/15 (13.3%) patients with positive margins plus additional excision at IFS and in 5/81 (6.17%) patients with negative margins at IFS (P = 0.32). The first report on the use of IFS during laparoscopic radical prostatectomy was published in 2003, by *Fromont et al.* (7). Laparoscopic intrafascial radical prostatectomy with IFS of postero-lateral margins was perfomed in one hundred patients. Positive margins were found at IFS in 24 pts. The neurovascular bundle was excised on the side of the positive margin. Residual tumor in additional resected tissue was present in 8 patients (33.3%) and absent in 16 patients. The Authors concluded that IFS analysis could significantly decrease positive surgical margins rate from 33% to 12% overall, and from 26.1% to 7.9% in pT2 tumors. ($p < 0.001$ and $P < 0.005$, respectively). No oncological followup was reported. *Dillemburg et al.* (6) performed laparoscopic radical prostatectomy and IFS in 198 consecutive patients. The specimens were obtained from the prostate apex, the bladder neck, and from neurovascular bundle or lateral pedicle soft-tissue in case of suspicious capsular incision; cancer was found at IFS in 12 (6%), 1 (0.5%), and 2 (1%) patients, respectively. In additional 42 patients (21.2%) benign prostate with no malignancy tissue was found. In all cases (15) of cancer positive IFS, extensive further tissue excision was performed in the area of the positive margin. The authors suggested that, according to low positive predictive value, IFS in the bladder neck and postero-lateral parts of the glands were no useful. However, at the apex IFS could decrease positive margin rate from 8.6% to 3.5%. Followup was just 3 months.

In another paper (8), 83 of 608 pts. underwent nerve-sparing radical prostatectomy. Intraoperative Frozen Section was performed due to a palpable lesion near the capsule on the postero-lateral aspect of the gland. In case of positive margin at frozen section, the ipsilateral neurovascular bundle was excised. Cancer was present in 93% of the IFS specimens. The Authors stated that with the use of IFS and subsequent ipsilateral bundle excision, in case of palpable lesions, overall positive surgical margin rate was reduced from 118/ 608 patients (19.4%) to 88/608 (14.5%) (from 38.2% to 28% in 123 pT3 tumors). In a paper from Memorial Sloan Kettering (19), IFS was performed in 259 patients, after careful examination of the prostate during surgery suggesting the likelihood of a positive margin. Cancer was found in 23 (8.9%) frozen section specimens, all confirmed on permanent section analysis. Conversely, 32 further positive margins were missed by IFS, with high specificity (100%), but low sensitivity (42%). Based on these data, the Authors concluded that routine IFS analysis of suspicious areas during radical prostatectomy is not expected to reduce the rate of positive surgical margins significantly.

In a recent literature review on IFS, *Ramírez-Backhaus et al.* (20) found that there was no consensus on use of frozen sections during radical prostatectomy, neither there was consistency in the technique, in the site and the clinical indications to perform it.

Few papers have really questioned or investigated to date which is the oncological advantage, if any, of PSMs rate decrease obtained with intraoperative frozen section. Recently a large retrospective series on 4217 open (3218) or laparoscopic (999) radical prostatectomies has been reported (5). Of 585 patients with positive margins, 98 who had PSMs on the specimen underwent resection of additional periprostatic tissue from the prostatic bed, due to concern of residual cancer, based upon visual inspection of the prostate specimen or in case of positive or close margin at IFS. Periprostatic tissue was sent from the prostatic bed in 98 patients, for routine analysis in 24 patients and for IFS with or without further tissue in 74 patients. In 74 pts. undergoing frozen section, 40 were positive and 34 negative for cancer. Overall, with additional tissue resection the Authors reported that 39/98 positive margins (39.7%) were rendered negative. 34 of 74 (46%) patients who underwent IFS were rendered

margin-negative with further tissue resection In patients with pT2 cancer, the mean 3-year biochemical recurrence -free probability was 97.9%, 89.0% and 100% for NSM, PSM, and PSM rendered negative, respectively. In patients with pT3 cancer, the mean 3-year biochemical recurrence -free probability was 83.7%, 73.7% and 90% for NSM, PSM, and PSM rendered negative, respectively. The Authors concluded that biochemical recurrence rate in patients with positive margins rendered negative, was similar to the one of patients with negative margins, and lower than biochemical recurrence rate in patients with persistently positive margins. They suggested a possible benefit of further tissue resection in case of intraoperative positive margins. However, several bias can be found in this paper. The study is retrospective and nearly 2% only of patients underwent further tissue resection. According to their results, there is a trend toward better biochemical survival for patients with positive margins rendered negative, compared to patients with negative margins, which seems quite difficult to understand.

In our study, all patients underwent IFS and additional tissue was always removed in case of positive margins. Intraoperative frozen section was obtained from prostate surface, which seems more logical, from all the areas where a positive margin is likely to occur: apex, bladder neck area, and postero-lateral aspect (21). It seems less rational to obtain tissue from prostatic bed, especially when a nerve-sparing procedure is planned, since further tissue excision could damage the neurovascular bundles in patients with negative margins. The 5-year followup in our study should be adequate to reveal a significant difference in biochemical recurrence rate (22). We have found no oncological advantage with IFS and further tissue resection in case of positive margins. Why should a wider excision not provide better cancer control? One explanation could be that additional tissue excision might be performed at an anatomic site not exactly corresponding to the positive margin on prostate surface. After gland removal, it is not easy to identify exactly all the locations of the prostatic bed corresponding to any specific prostate area.

Another point could be that patients with positive margins might be at higher risk of distant metastases (23), thus compromising the oncological effect of further excision. Our series has not the statistical power to assess disease recurrence according to extent and site of positive margins. However this subclassification seems not always useful in predicting cancer recurrence (24). The only group of patients where no definitive data could be drawn where the ones with pT2 cancer. In these patients, a positive margin might be iatrogenic and correlated to a capsular incision. A focal capsular incision is not always associated with a worse prognosis (25). On the other hand, these patients represent a more favorable prognostic group, and simply follow-up could be not long enough to detect a recurrence difference between positive, positive rendered negative, and negative margins.

Conclusions

To date this is the largest series, with longest follow-up, on the results of frozen section and further tissue resection in case of positive margins, during radical prostatectomy.

We have clearly demonstrated that Intraoperative frozen section with additional excision in case of positive margins doesn't provide any benefit in terms of cancer recurrence, also in cases with no residual tumor on the resected specimen.

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ORIGINAL PAPER

Orthotopic neo- bladder in women.

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Summary

Introduction: *Radical cystectomy is the most effective treatment madality for high grade urinary bladder carcinoma and orthotopic reconstruction is the better urinary diversion modality also in women.*

Material and methods: *From 2002 to 2007 we performed 14 radical cystectomies followed by orthotopic reconstruction in women aged between 47 and 68 years (mean age 56) affected by urinary bladder carcinoma. Our reconstructive technique requires the preparation of two strips of the recti muscles fascia, the sectioning of the bladder neck and, when the uterus is present, hysteroannessiectomy and cystectomy en block leaving intact the lateral and inferior vaginal walls. The pelvic floor is stabilized by a colposacropexis with a prosthesis and placing an omental flap over the prosthesis The orthotopic reconstruction is achieved via a neobladder according to the Padovana technique. The ureters are anastomized to the neobladder and splinted with single J stents.*

Results: *The pathological examination demonstrated in all patients the presence of a high grade carcinoma (G3): more specifically 4 patients had a full thickness intramural infiltration (T2), 2 patients had involvment of the perivescical fat (T3) ad 8 patients were in T1 stage. Lymphnodes were negative for tumour (N0). In 8 patients blood trasfusions were necessary to treat post surgical anemia. No significant intra-, peri- or post operative complications were noted. The mean follow-up was 45 months: a patient died for diffuse metastatic disease after 11 months. The remaining patients are still alive and report normal lifestyle: 10 with normal micturition and 4 with urinary retention treated with intermittent self-catetherization. Two patients report nocturnal incontinence treated with hourly micturition and one pad. The five patients who had normal preoperative sexual intercourse resumed a normal sexual activity.*

Discussion: *The possibility to orthotopically recontruct the female urinary bladder has been established long time after the introduction of orthotopic neobladder in males, when became obvious that bladder reconstruction had to be done in conjunction with the recostruction of the pelvic floor, in order to assure a satisfactory function af the new bladder. To avoid a posterior slippage of the vaginal stump we inserted the vaginal stump into a prolene tube which was then anchored posteriorly to the sacral periostium. We covered the prolene net with a flap of omentum pedicled down from the transverse colon and brought into the pelvis through the right colic space. This solid, stable and well protected support was able to accept the new bladder. We use the Padovana technique to facilitate the anastomosis of the bladder neck to the urethra. In the patients affected by uretrhal ipermotility we shaped a sub urethral sling using the recti muscles fascia pedicled by the pyramidal muscles. With this modality of reconstruction female pelvic anatomy is preserved as demonstrated by recovery of sexual activity.*

KEY WORDS: *Cystectomy; Orthotopic ileal bladder; Bladder tumour.*

Submitted 8 October 2010; Accepted 30 October 2010

INTRODUCTION

Radical cystectomy is the most effective modalty of treatment for the high grade urinary bladder carcinoma. Orthotopic reconstruction is the preferred method for urinary diversion in the male patient; the increased knowledge of the urethral anatomy and some improvements in the surgical reconstructive technique allowed to extend the option of orthotopic reconstruction of the urinary tract also in the female (1). Because of these advances adequate reconstruction can follow radical surgery and at the same time allow an excellent recovery of bladder function.

Figure 1.
The "Tube" shaped prosthesis for the colposacropexy.

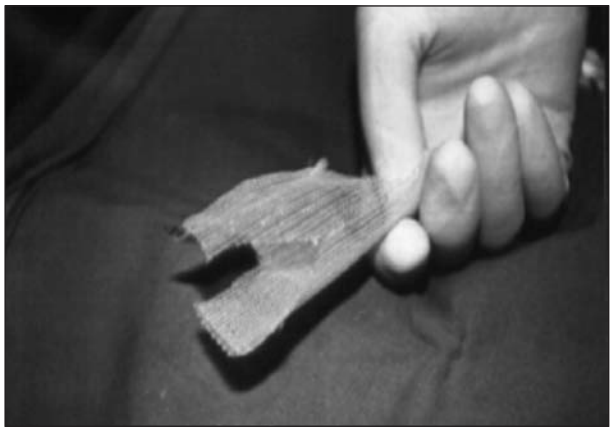
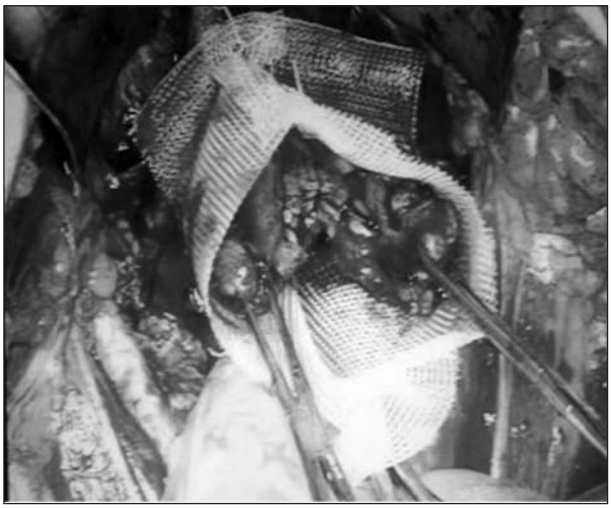


Figure 2.
The vaginal stump is inserted into a prolene prosthesis.



Material and methods

From 2002 to 2007 we performed 14 radical cystectomies followed by orthotopic bladder reconstruction in women aged between 47 and 68 years (mean age 56) affected by urinary bladder carcinoma.
Diagnosis was histologically established after transurethral bladder resection (TURB) and eight patients were submitted to intravescical immunotherapy with BCG prior to surgery. All the patients were studied with abdominal and pelvic computed tomography (CT) scan and with bone scan. None was found to have pathological enlarged lymphnodes, bone metastasis or involvment of the adjacent organs. In one patient who had been treated with BCG the bladder lining was found negative with 2 biopsies done after 2 months. One patient had been treated with radical hysterectomy for carcinoma of the portio 25 years before.
Our technique requires the preliminar preparation of 2 strips of the recti muscles fascia: these pedicles arise distally to the pyramidal muscles and are to be used at the end of the procedure to shape a sling to be placed under the urethra. The sectioning of the urethra is performed close to the bladder neck after the creation of a cleavage plane between the urethra itself and the vagina to allow to suspend the cervical region. When the uterus is present an hysteroannessiectomy and cystectomy en block is performed leaving intact the lateral and inferior vaginal walls. After closing the vaginal stump the pelvic floor is stabilized by a colposacropexis with a prosthesis (2) (Figure 1, 2) placing an omental flap over the prosthesis (Figure 3). The orthotopic reconstruction is achieved via a neobladder obtained from 45 cm of detubularized terminal ileum reshaped according to the Padovana technique (3) (Figure 4). The ureters are anastomized to the neobladder and splinted with single J stents. The new reservoir thus created is anastomosed to the urethral stump and placed over the pelvic omentoplasty which is suspended over the prolene prosthesis of the colposacropexis.

Results

Pathological examination confirmed in all the patients the presence of a high grade carcinoma (G3): more specifically 4 patients had a full tchikness intramural infiltration (T2), 2 patients had involvment of the perivescical fat (T3) ad 8 patients were in T1 stage. Lymphonodes were always

Figure 3.
The omental flap peduncolized from the transverse colon.

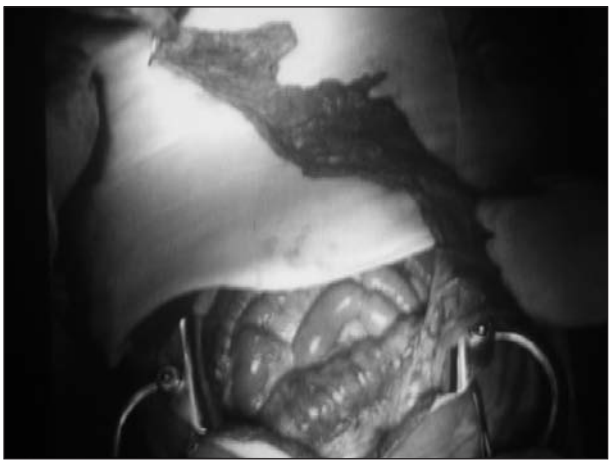
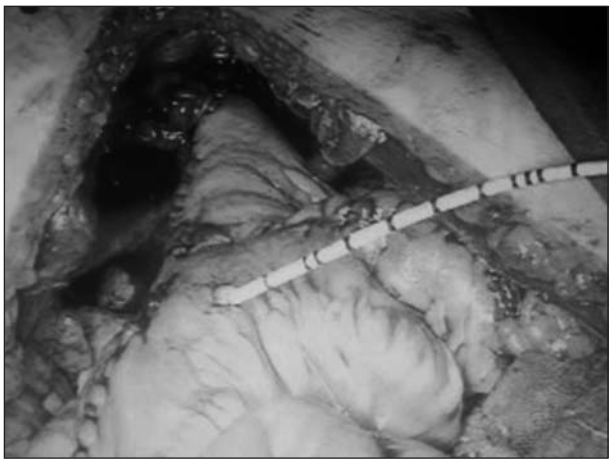


Figure 4.
The final reconstruction of the vescica ileale padovana.



negative for tumour (N0) although no lymphnodal dissection was performed in the patients who had been treated with radical hysterectomy (Nx). In 8 patients blood trasfusion were necessary to treat post surgical anemia. All patients received antibiotic profilaxis for 10 days by cephalosporins anticoagulant therapy with low molecular weight heparin for 20 days. The nasogastric tube was left in for an average of 5 days. The ureteral catheters were left in for an average of 12 days (10-16); the vesical catheter has been always removed on the 21st post op day. Abdominal peristalsis resumed promptly in all patients and normal bowel evacuation resumed after 4 to 8 days. No significant intra-, peri- or post operative complications were noted.
The mean follow-up was 45 months: one patient died from diffuse metastatic disease after 11 months.
The remaining patients are still alive and report normal lifestyle: 10 report normal micturition and 4 have urinary retention treated with intermittent self-cateterization. Two patients report nocturnal incontinence treated with hourly micturition and one pad. The five patients who had normal preoperative sexual intercourse have resumed a normal sexual activity.

Discussion

The possibility to orthotopically recontruct the female urinary bladder has been established a long time after the introduction of orthotopic neobladder in males. This is due to the smaller number of cases of severe bladder patology in women, and to the incomplete knowledge of the anatomy of the female urethra. Afterwards, as the procedure begun to be established, it became obvious that it has to be associated to the recostruction of the pelvic floor, in order to assure a satisfactory function af the new bladder. Of fundamental importance for the aquisition of knowlwdge of the anatomy and physiology of the bladder were the studies of *Colleselli and Bartsch* (1, 4) in the mid 90's: they make clear that radical surgery could be done by sparing the urethra and so preserving continence. These authors established that the recurrence of urothelial cancer in the urethra is a rare occurence (5) and that the proximal third of the urethra could be removed without damaging the sphincter function (1, 4, 6).
Of great importance as well was the discovery of the innervation of the urethra running in the lateral vaginal walls: *Stenzl and Hautmann* (4, 6) teorized that these walls need to be spared in order to avoid to denervate the urethra and compromise continence. In particular we have also established that the vagina constitutes the fulcrum of the new pelvic arrangement. Stenzl anchored the newbladder to the pelvis in order to avoid the posterior prolapse (4) and we assumed this evidence for our technique.
The anatomical sparing of the urethra is easily obtained due to the wide space of the female pelvis and we routinely spare the lateral vaginal walls to allow for the preservation of the urethral innervation.
According to our personal experience we have modified the technique to avoid the posterior slippage of the vaginal stump described by *Timmons & Addison* (2, 7): our method grants a good pelvic stabilization by inserting the vaginal stump into a prolene tube which is then anchored posteriorly to the sacral periostium. The implant of prosthetic material into the pelvic area could stimulate adhesions or erosion into the new bladder: in order to avoid it we cover the prolene net with a flap of omentum pedicled down from the transverse colon and brought into the pelvis through the right colic space. A solid, stable and well protected support was created to accept the new bladder. The interposition of the omentum has also the purpose to avoid another possible important complication of the neobladder in the woman that is the formation of a fistula between vagina and neobladder (8).
We prefer the Padovana technique (3) to facilitate the anastomosis of the bladder neck to the urethra avoiding extreme traction on the new loop.
This new reservoir, like all the intrabdominal ones, empties in response to an increase of the intrabdominal pressure that needs to act upon a stable base (9). In 4 patients we have urinary retention due to excessive urethral correction or to the formation of a "*floppy bag*". Another debated topic is the risk of stress incontinance in patients affected by this problem before surgery: in these patients we shaped a suburethral sling using the recti muscles fascia pedicled on the pyramidal muscles. In other cases the correction of the problem can be obtained afterwards with an eterolougous sling or with urethral bulking. This modality of reconstruction respects female pelvic anatomy as attested by the preserved or regained sexual activity.

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REVIEW

The use of the hyperbaric oxygenation therapy in urology.

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Summary

The basic principle of the hyperbaric oxygenation therapy (HOT) is to increase the dissolved oxygen in the blood when it is administered at high pressure. Then O_2 will be distributed to the tissues through the pressure gradient, in this way obtaining an hyper-oxygenation of the tissue that has anti-inflammatory and pain-killing effects and induces augmentation of bacterial permeability to the antibiotics, neo-angiogenesis, enhancement of lymphocytes and macrophages function, augmentation of the testosterone secretion (in male), and healing of wound.

These positive effects can be used in urology in several conditions: Scroto-perineal fascitis; Radiation-induced cystitis (and proctitis); Interstitial cystitis (urgency-frequency syndrome); Chronic pelvic pain.

Our experience and the specific literature on this subject, suggest that HOT, sometimes associated with other medical and surgical therapies, can be a useful tool for treating such urologic diseases; in some cases this use is codified (Fournier's gangrene and Radiation-induced cystitis) in others (urgency-frequency syndrome and chronic pelvic pain) it represents a promising technique and needs further research.

KEY WORDS: *Hyperbaric oxygenation therapy; Necrotizing fascitis, Radiation-induced cystitis.*

Submitted 25 April 2010; Accepted 30 October 2010

INTRODUCTION

The hyperbaric oxigenation therapy is used in some urological diseases. The basic principle of this therapy is the tissue hyperoxigenation obtained by the increase of the diluted oxygen in the blood. Normally the haemoglobin is saturated by oxygen up to 98% and this level of saturation can't be increased; to improve the amount of diluted oxygen in the blood it is necessary to administer it at high pressure. Oxygen increases by 10-13 times (1) and this high amount of oxygen is distributed to the tissues with a pressure gradient (2).

The hyperoxygenation has an anti-inflammatory effect and favors tissue regeneration, recovery and healing (3, 4).

The hyperoxygenation moreover improves local synthesis of the growth factors, particularly *fibroblastic growth factor* (FGF) and *vascular endotelial growth factor* (VEGF) (5) which improves the neoangiogenetic process (3, 6). Furthermore hyperoxigenation regulates production of *tumor necrosis factor* (TNFa), reduces synthesis of PGE2 and COX-mRNA (2), enhances the limphocytic and macrophagic functions (2, 7, 8) and, finally, increases bacterial permeability to antibiotics (2, 4, 9, 10). The use of the hyperbaric oxygenation therapy in urology is definitely accepted in the treatment of the *Fournier's gangrene* and radio-induced cystitis and rectal bleeding (2).

For interstitial cystitis, urge-frequency syndrome and chronic pelvic pain this therapy is still experimental.

FOURNIER'S GANGRENE

This disease is a necrotizing fasciitis which affects the fascial plains of the scrotum and perineum, but it can affect also groins until the flank and ischiatic regions (11).

It presents in patients with immuno-deficienct conditions (diabetes, ethilisms chronic degenerative diseases) and develops from urethral, anal or dermatologic diseases (12).

The isthology shows an inflammation of the fatty subcutaneous tissue, with oedema, endo-arteritis and thrombosis creating necrosis of tissues (12).

Near the necrotic areas appears an extended panniculitis

which secretes an exudate, which contains toxic cytokines. The microbiologic ethiology is complex and multimicrobial: *Staphylococcus, Streptococcus, Clostridium etc.* (11, 13).
The mortality rate ranges between 7 to 60% (14, 15).
Necrosis and panniculitis extension and numerous metabolic parameters (most importantly renal function) are the prognostic factors (16).
Early treatment improves the prognosis (12)and reduces the extension of surgical demolition (13).
The therapy of the *Fournier's gangrene* includes multiple methodologies such as surgery, advanced dressings and hyperbaric oxygenation therapy with daily 90 min long sessions, for 30-40 sessions at 2,5 ATA (atmospheres absolute). General and metabolic therapy are associated and also antibiotics (12, 13, 17).
When the acute phase is resolved, it is possibile to cover the destroyed regions with cutaneous flaps (18, 19).
The hyperbaric oxigenation therapy supports the therapy of the *Fournier's gangrene* during the initial therapeutic phases and during the reconstructive therapeutic period, because it reduces inflammation and has an antimicrobial action, promoting the tissues regeneration and rooting of the flaps (2, 6). The use of the hyperoxigenation in this syndrome isn't proven with statistical evidence, but the efficiency is confirmed by numerous empirical data obtained from frequent clinical use.

Radiation induced cystitis

Radio-therapy in urology is mainly used to treat prostate cancer as a radical therapy as well as after a radical prostatectomy (20). Actually it is performed with conformational methodology to reduce exposed areas to radiation, nevertheless radio-induced inflammation of the bladder and rectum can occur.
The radio induced cystitis can appear during radiotherapy or a long time after therapy (21).
The histology presents the oedema of the mucosa of the bladder with inflammation of the lamina propria. This kind of cystitis can be healed or can evolve into subacute or chronic disease (21).
In this case the histology shows occlusive arterial thrombosis with epithelial necrosis and mucosal bleeding and fibrosis of the smooth muscle cells (21). The most important clinical aspect is the persistent and recurrent hematuria with urge, frequency and disurya (21). This cystitis is staged with a scale (2). The epidemiology is not well defined because numerous mild cases are not even reported but actually the clinically manifested cases are reduced from 20% to 5% of the patients treated with conformational radiotherapy (2).
In these cases the hyperbaric oxygenations is largely used and commonly 40-60 sessions 90 min long at 2,5ATA are carried out.
It causes a reduction of the tissue inflammation (4), reduces the capillary pressure with reduction of the oedema, promotes the healing process and amplifies fibroblastic activity and neoangiogenesis (2, 22).
Several Authors report the hyperbaric oxygenation therapy as beneficial in the recovery of long-term hematuria (2, 22-25) and irritative micturitional symptoms (23). As in cystitis, the radioinduced proctopathy is treated with hyperbaric oxygenation that reduces tenesmus and rectal bleeding (26, 27).
Generally it is suggested an early start of the hyperbaric oxygenation after radiotherapy, but this topic is still debated (28).
Finally it is important to note that neo-angiogenesis caused from the HOT doesn't induce the recurrence of the prostate cancer (8, 29).

The interstitial cystitis and urgency/frequency syndrome

These two conditions present a clinical pattern with pelvic and urethral pain, micturitional urgency/frequency, negative microbiological urinary culture, negative urine citology, haematuria; the morphological aspects are less defined, in fact the classic interstitial cystitis with Hunner's ulcer, is rare (30), and often the diagnosis is based on the association of clinical, endoscopic (glomerulations) and urodynamics aspects (31).
The therapy aims to reduce the inflammation of the bladder and therefore the symptoms (30, 31); in the case of the Hunner's ulcer a surgical procedure with augmentation ileocystoplasty is needed (30).
The interstitial cystitis and the urgency/frequency syndrome have some clinical and morphological analogy with radioinduced cystitis and so some Authors have tried to treat also it with hyperbaric oxygenation therapy.
In fact hyperbaric oxygenation due to its antinflammatory effect and the activation of the angiogenesis and healing processes can improve the symptoms, in particular in cases presenting with glomerulations (7, 32).
The therapy consists of 30-40 sessions 90 min long at 2,5 ATA.
The series are limited in number but the results are interesting with improvement of frequency, urgency and pain for 15-24 months (7, 32); these results are based on self-evaluation from the patients and therefore could be related to both placebo or therapeutic effect (placebo is effective in this syndrome up to 30% of cases) (33). On the contrary it is almost impossible to evaluate the changes of the histological aspects.
For this reason the use of hyperbaric oxygenation in these syndromes should be validated by further research.

Chronic pelvic pain syndrome

The clinical analogy between the chronic pelvic pain syndromes and interstitial or radioinduced cystitis, suggests to propose the hyperbaric oxygenation also for the treatment of this disease.
The chronic pelvic pain is a condition of pelvic, perineal, testicular or hypogastric, chronic or relapsing pain (34).
The ethiology and physio-pathology are unknown
The EAU guidelines identifies two groups of patients with chronic pelvic pain: one includes patients with defined diseases (such as prostatitis) or with a morpho-anatomic equivalent (endometriosis, anal diseases etc.) and another including the patients with the idiopathic forms which have the same sites of pain in common (34).

Regarding the first group the hyperbaric oxygenation can operate against the inflammation and also promote the reduction of the symptomatology. To explain the effect of the hyperbaric oxygenation in the second group is more difficult; we can hypothesize that hyperbaric oxygenation modulates the synthesis of the growth factors and PGE promoting some local and central pain-killing effects.
Hyperbaric oxygenation is used to treat chronic pain syndromes affecting different somatic tracts, with encouraging results (10, 35), therefore extensive research including urologists, gynecologists and hyperbaric specialised physicians, should be promoted in order to integrate this therapy with the other numerous treatments for chronic pelvic pain syndromes.

Conclusion

Our experience with the use of the hyperbaric oxygenation therapy in urology is based on 22 patients treated for *Fournier's gangrene*, 8 patients treated for radiation induced cystitis and 4 patients treated for urgency/frequency syndrome (after approval of ethical committee). In consideration of our promising preliminary results, we can conclude that the hyperbaric oxygenation therapy interferes in the tissue metabolism, has an anti-inflammatory effect, and also promotes neo-angiogenesis, tissue repair and healing; in urology this therapy seems to offer promising prospectives and in fact its use is confirmed for radio-induced cystitis and rectal bleeding and for necrotizing fasciitis.
In other fields of the urology – such as urgency/frequency syndromes and chronic pelvic pain syndromes – it would be interesting to extend the research to better understand if this therapy can reduce the symptoms and can improve the efficacy of multimodal therapies and promote the hyperbaric oxygenation therapy on the basis of more solid findings.

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REVIEW

Cerebellar pathology and micturitional disorders: Anatomotopographic and functional correlations.

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Summary

Cerebellar diseases represent about 2-3% of neurologic pathologies; they usually are classified as:
– heredodegeneratives
– pure cerebellar syndromes.
Such diseases – aside from their aetiology – lead, through several evolutive stages, to different micturitional disorders,in most cases represented by hyperreflexic non dyssynergic bladder and urinary incontinence.
On the basis of anatomopathological studies, also considering our 16 years long personal series (1992-2008), we were able to establish a relationship between such disorders and specific cerebellum anomalies, mostly of Purkinje network.

KEY WORDS: Cerebellum; Urinary incontinence; Purkinje cells.

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INTRODUCTION

Heredodegenerative or acquired cerebellum injuries are a peculiar chapter of neurological pathology, representing 2 to 3% of all neurological pathology itself.
They are quite unusual and polymorphous by the clinical, symptomatological and mostly neuro-anatomical point of view. As a matter of fact, spinal cord, cerebellum, cerebral bulb, pontis nuclei, mid brain and therefore the whole medulla oblongata can be variously affected. More recent studies have confirmed – thanks to anatomopathology advances – that cerebellum is first affected, other nervous structures being affected only later.
The aim of our study is to establish a relationship between pure urological disorders and anatomopathological injuries of the cerebellum alone, so stressing once for ever the exact important role of cerebellum micturitional dynamics.

MATERIALS AND METHODS

From 1992 to 2008, with the cooperation of *C. Besta Insitute of Neurology of Milan* and of the *Neurology* and *Urology Depts of Niguarda-Ca' Granda Hospital of Milan*, we studied 75 patients (50 males and 25 females), aged 48 to 67: all of them were affected by pure or heredodegenerative cerebellum injuries, connected with micturitional troubles. Videourodynamic investigation, together with electrophysiological study of perineum vs electromiography (EMG), was the main examination.
In order to complete diagnosis, the patients also underwent uroflowmetry with ultrasound evaluation of post-micturitional residual urine, urinary tract ultrasonography, kidney nephroscintigraphy.
From the neurological point of view, the patients underwent clinical evaluation, somatosensory evoked potential (SEP), cortical evoked potentials (CEP), liquor test and magnetic resonance imaging (MRI scan).
Twelve patients who died for other reasons underwent autopsy.

RESULTS

Urinary symptoms can be summarized as following:
– frequency-nocturia 73%;
– urinary incontinence 84% (of which: motor incontinence 75% and sensory incontinence 25%);
– hesitancy 18%;
– urinary tract infection (UTI) 11%;
– detrusor/sphincter dyssynergia 3%.

Erectile function was not fully investigated; only three patient however complained of sexual disturbances. We although must remember that these patients were also affected by correlated pathologies, like diabetes mellitus, arterial hypertension, hypercholesterolemia and that probably sexual impairment is connected with the above mentioned pathologies rather than with true neurological problems.
On the 75 urovideodynamic investigations performed we were able to obtain the following results:
– hyperreflexic non dyssynergic neurogenic bladder in 59 cases (78,6%);
– neurogenic bladder with detrusor/sphincter dyssynergia in two cases (2,6%);
– in the remaining 14 patients non inhibited detrusor contractile waves (18,6%), non inhibited contractions (CNI) arised at reasonable filling volume (200-310 ml); and later on a "delayed" hyperreflexic pattern developed with different timing and modality.

According to a International Continence Society (ICS) validated protocol, pharmacotherapy with oxybutynin chlorohydrate was carried out, together with sterile intermittent catetherisation when needed (high risk for upper urinary tract impairment). PES, PEC and EMG do not prove to be selective as we already stressed in other previous papers.

Neuroanatomy reminder

Taking into account relationships and functions of the different parts of cerebellum, we can recognize those areas that appear at different phylogenetic stages, showing different development and function. These areas can be located both at cortex level and in intrinsic nuclei: they are called respectively Archi-Paleo and Neocerebellum.
Cerebellum neuroanatomy can so be classified by the three following systems:
1) ascending system to cerebellum: it includes the spinal, trigeminal, reticulovestibular olivary and pontine afferences;
2) intracerebellum connexion system, formed by the Purkinje cells neuritis, that are directed towards the cerebellum nuclei, making synapsis with the nuclei of the tectum, with it's globose and emboliphorm shape, and with the nucleus dentatum;
3) ascending system to cerebellum formed by efferences of the median area of the cauda (or flocculonodular lobulus), of the intermedious and lateral areas.

The correct achievement of fine or rough movements not only needs adequate muscular strength (concerned muscles and nerves must be undamaged), but also the harmonization of the following phases of the movement itself (direction and extension). Deep sensibility patways, vestibular patways and the cerebellum itself are responsible of these complex functions.
Electrophysiological studies show that Purkinje cells are the only way out from cerebellum for inhibitory and restraining impulses. These cells for istance receive facilitatory drives from climbing fibres and inhibitory impulses from the Golgi cells, from stellate and basket cells. An electrical system is so organized; its central nucleus are the Purkinje cells, carrying tipical inhibitory activity, being though modulated by other excitatory or inhibitory cells that recognize their origin in various cerebellar archistructures. As previously said, cerebellar cortex is divided in three layers: in the intermediate layer the

Figure 1.
Cerebellum cortex: normal Purkinje cells.

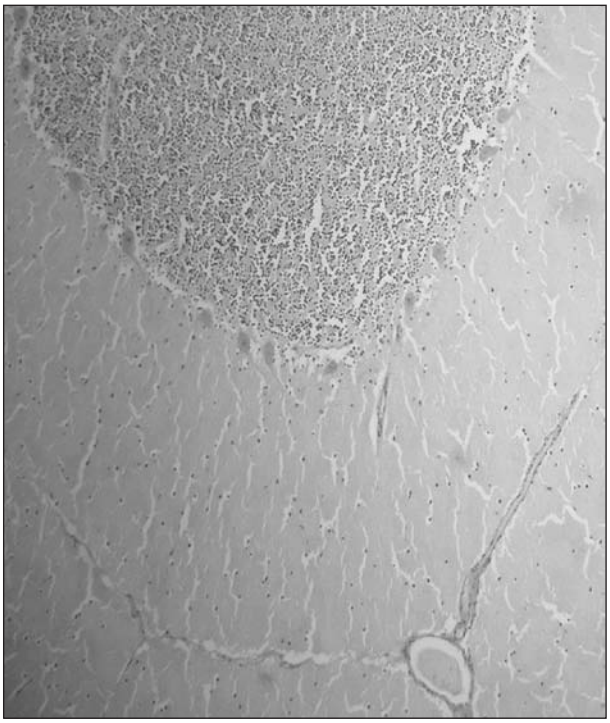
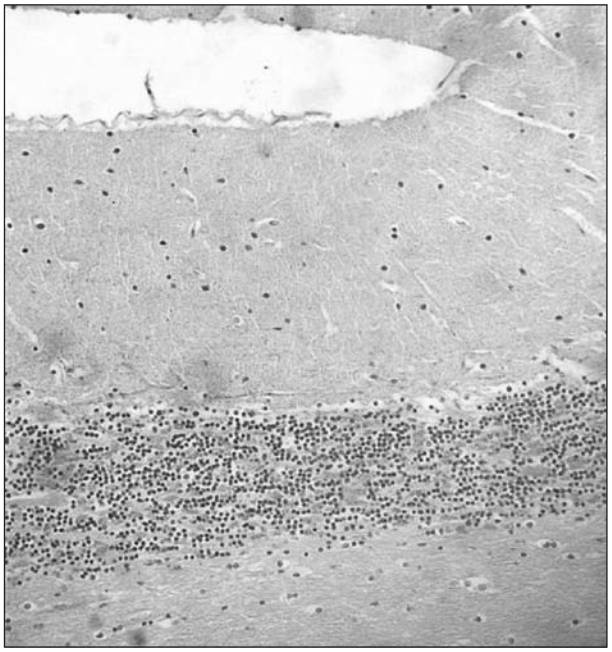
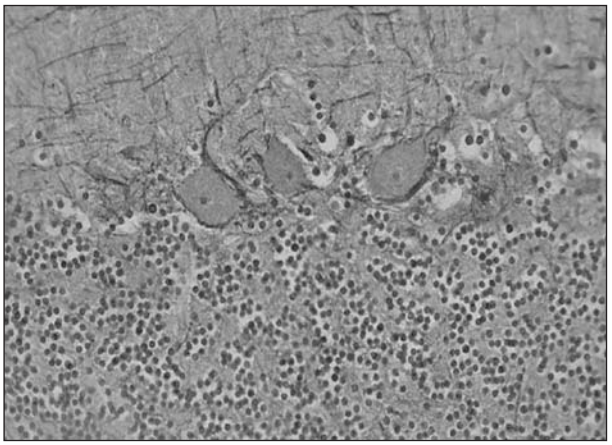


Figure 2.
Cerebellum: no Purkinje cells.



Purkinje cells can be found, regulary set in an only row.
The dendra widely ramify, whereas the neuritis stop at the vestibular or cerebellar nuclei. The terminal stations are so constituted by the alpha and gamma spinal cord motoneurons and by the brainstem neurons.
The cerebellar afferences allow – by means of the reticular substance – to reach the spinal cord, i.e. the spinal micturitional centre so allowing the inhibitory drive to reach the bladder.
From the anatomopathological point of view a short tinning with strong gliosis of these cells can be seen.
Such a phenomenon hasn't reparative function; it's nature is first isomorph, later anisomorph until a "monstre" gliosis is reached.
In the hereditary forms, instead, the vasculo-hereditary cause is well known; still uncertain seems to be the the causal factor in the pure cerebellar syndromes.

Figure 3.
Cerebellum cortex: Purkinje cells with gliosis.



Discussion and conclusions

As previously stressed, the Purkinje cells is the only cerebellum afferent patway. Their activity are expressed by inhibitory drives that (by means of other descending nervous structures – pyramidal/extrapyramidal system) not only reach the pontine micturitional centre, but also the medullar centre itself, so allowing bladder filling. Autoptic studies show rarefaction of these nervous elements due to several causes, apart from which the outcome is the gliosis, a reparative-like tissue, completely afunctional from the electrical point of view. Such condition could probably explain the onset of bladder inflammatory symptoms, that can led to incontinence.
According to *Hoebeck et al.* (1) the tinning of this cellular set, also shown by the decrease of synaptic junctions of these cells, would be able to increase some anomalies in impuls transmitting and to increase on the other hand, the discharge frequency of the cerebellar nuclear structures.
Another paper by *Sarna et al.* (2) establishes a connection between the normal cellular topography of Purkinje cerebellar cells and it's relationship with cerebellar cortex. This study takes then account of the different pathologic patterns, like ischemia, infections, toxicity and mainly heredodegenerations. This paper joins together the whole literature concerning Purkinje cells pathology, so connecting it with normal cerebellar topography.
Experimental studies by *Dusart et al.* (3) point out three different kinds of anomalies of Purkinje cells: apoptosis, autophagy (both frequent) and necrosis (unfrequent).
Same important results in studying this cellular pathology came from *Igarashi et al.* (4), who studied the cellular changes of some brain (cortex, Ammon's horn, latero dorsal thalamic nuclei) and cerebellar areas, with peculiar care to cortex and Purkinje layer. Following certain pathologic events, for istance trauma or vascular agents, the first event provoking the pathogenecic mechanism is hypotension and so anoxia. Such condition would then led to anoxic degeneration. Very important seems to be the activation – by Purkinje cells – of some mechanism finally leading to gliosis.
According to the results obtained by *Laurence et al.* (5) and by *Roda et al.* (6) the clinical conditions above mentioned explain the irritative symptoms complained by the patients, but mostly the videourodynamic patterns, giving evidence to the complete lack of the inhibitory control mechanism. The different polymorphism at the onset pattern must be related to the different degree of gliosis established within cerebellar structure (7).
The analysis of our series casistics corroborates the data obtained by other Authors, mostly from the diagnostic and therapeutic side. Videourodynamic investigation is a basic step in diagnostic and operational approach to these patients (8-10).
On the other hand electroencephalography (EEG) and MRI show to be aspecific, having instead more effectiveness in discriminating vascular, neoplastic and/or flogistic pathologic conditions.
It can so be stated that neurologic examination still represents the main help for correct diagnosis of these pathologies. The literature reviewed does not report therapeutic approaches different from the known.
Clean self intermittent catetherisation – with or without anticolynergic medication – allows a better management of these problems, as later proved by nephroscintigraphic data: only four patients showed accumulation.
The new therapeutic methodologies offer indeed new chances particulary in the unfrequent cases of detrusor/sphincter dyssinergia.

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CASE REPORT

Fibromuscular dysplasia causing renal artery aneurysm and renovascular hypertension: A case report.

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Summary

Objective: *Renal artery aneurysm is a rare disease and usually is due to fibromuscular dysplasia. We describe a case in a woman who had renovascular hypertension due to aneurysm of fibromuscular dysplasia-associated renal artery.* ***Material and methods:*** *The clinical presentation, renal function, radiologic data, complications and treatment were studied.* ***Results:*** *To report a case of 37-year-old female with a history of hypertension in the last year in pharmacological therapy and in absence of other clinical symptoms. A Doppler ultrasound and a spiral tomography revealed the presence of a right renal artery aneurysm with a hypoplastic kidney. Controlateral kidney was normal. We carried out total nephrectomy to resolve high blood pression and the risk of rupture. The patient was discharged home in 5th post operative day. Serum creatinine level remained normal as it was before. Her blood pressure normalized over a period of several months using a single antihypertensive medication.* ***Conclusion:*** *We suggested that in presence of renovascular hypertension in young adult fibromuscular dysplasia-related renal artery aneurysm will be suspected. When possible aneurysmectomy and angioplastic renal artery closure or segmental renal artery reimplantation and renal artery bypass are the gold standard while nephrectomy will be reserved for unreconstructable renal arteries or advanced parenchymal disease.*

KEY WORDS: *Fibromuscular dysplasia; Renal artery aneurysm; Renovascular hypertension.*

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INTRODUCTION

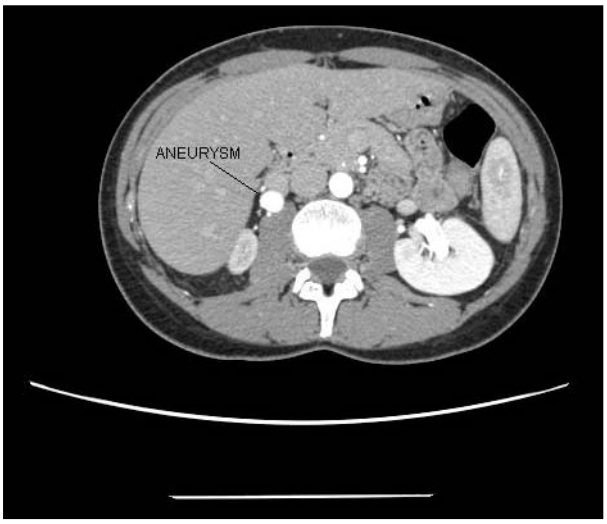
Renal artery aneurysm is a rare disease occurring in approximately 0,09% of the general population (1) and usually is due to fibromuscular dysplasia. It is a non-atherosclerotic, non-inflammatory vascular disease, responsible for 10-30% of cases of renal artery stenosis (2-3). Fibromuscular dysplasia may involve any layer of a visceral artery, and it may be classified as intimal, medial or adventitial. The medial form may result in arterial stenosis causing organ ischemia or infarction. Clinical symptoms of renal artery aneurysm are frequently high blood pressure, abdominal pain and hematuria. This pathology is often an incidental finding, as more frequently Doppler ultrasound, computed tomography (CT), magnetic resonance (MR) imaging and arteriographic studies are being performed for other diseases. Selective renal angiography remains the gold standard for the diagnosis of renal artery aneurysm. However, non-invasive diagnostic techniques such as Doppler ultrasound, MR angiography and CT angiography have proven to be accurate in assessment of renal artery aneurysm and provide valuable alternatives to diagnostic angiography (4-5).

The clinical features and management of renal artery aneurysms have generally been reported through case series depicting small numbers of patients (6-7). The treatment of choice of these aneurysms is not yet defined: particularly, what size renal artery aneurysm warrants surgery, when and how to repair them, how to follow those not treated surgically, and whether renal artery aneurysms cause hypertension or merely are associated with elevated blood pressure remain ill-defined issues.

CASE REPORT

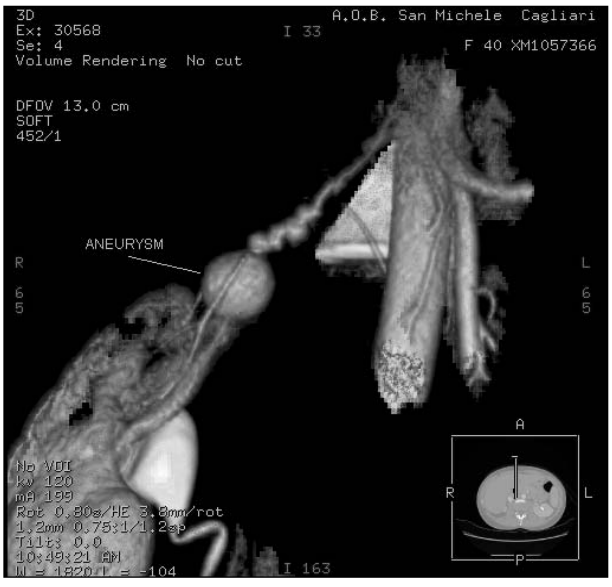
A 37-year-old female was admitted in our hospital because in the course of investigations for hypertension (for the

Figure 1.
Spiral CT showing right renal artery aneurysm.



duration of a year), an abdominal ultrasound revealed incidentally a right renal artery aneurysm with a hypoplastic kidney. We completed the examination with Doppler ultrasound and a spiral CT (Figure 1) that confirmed the presence of a diffusely hypoplastic right renal artery with a saccular aneurysm of 18 mm. in diameter in its middle third and two pielic branches originated from the upper pole of the aneurysm and the surrounding. The spiral CT also revealed the typical fibromuscular dysplasia lesion which is characterized by its classic "*string of beads*" appearance, consisting of alternating areas of narrowing and dilatation, located in the middle portion of the lower right renal artery (Figure 2). Controlateral kidney was normal. The patient

Figure 2.
3D spiral CT showing renal artery aneurysm and the "string of beads" appearance typical lesion of the fibromuscular dysplasia.



denied any family history of hypertension. Her physical examination revealed a blood pressure of 130/85 mmHg (hypertension was documented with a first-encounter mean blood pressure of 155/100 mm Hg). Her cardiovascular, respiratory, and central nervous system examinations were unremarkable. No evidence of retinopathy on fundus examination. There was no carotid, abdominal or femoral arterial bruits. ECG, chest radiograph and echocardiography were normal. Her blood urea nitrogen and serum creatinine were within normal limits. Percutaneous transluminal angioplasty and "*in situ*" techniques were considered seriously but assessed as inappropriate because of coexistent numerous kinking and twisting of renal artery and involvement of branch arteries. Also in consideration of the advanced parenchymal disease we carried out total nephrectomy to resolve high blood pression and the risk of rupture. The patient was discharged home in 5th post operative day. Serum creatinine levels remained normal as it was before. Her blood pressure normalized over a period of several months using a single antihypertensive medication (losartan 50 mg once daily) rather than 2 medications, and now no longer required any medication. Pathological examination confirmed the presence of renal artery fibromuscular dysplasia.

Discussion

In most cases (until 90%) these aneurysms are of fibrodysplastic origin while acquired or postoperative aneurysms accounted for only 10% of cases (8).
Dysplastic aneurysms are usually saccular with a fibrous neck and are located at or near an arterial bifurcation, they may have a very thin wall that explains the possible occurrence of rupture or dissection; rupture is unlikely in most patients, intrasaccular thrombosis is very rare and so are embolies in the kidneys. Associated lesions are present in about two thirds of the patients and require a complete evaluation before surgery: lesions of the renal artery (segmental stenosis or diffuse fibromuscular hyperplasia) are the most frequent other arteries either in the abdomen (aorta, splenic) or in distant territories (carotid) may also exhibit pathologic changes, particularly aneurysms; lesions of the kidney(s) and/or of the urinary tract may also be observed. In 80% of patients, the aneurysms were discovered on angiography performed because of arterial hypertension. But 20% of the patients were strictly normotensive. Fibromuscular dysplasia usually affects females between 15 and 50 years of age, frequently involves the mid or/and distal segment of the renal artery and is bilateral in 2/3 of the patients (9). Renal artery stenosis secondary to fibromuscular dysplasia may affect pregnant women and thus remains an important consideration as a cause of secondary hypertension during pregnancy. Renovascular hypertension is the consequence of renin-angiotensin-aldosterone system activation as a result of renal ischemia. Unilateral renal ischemia initiates an increased secretion of rennin, which accelerates the conversion of angiotensin I to angiotensin II and enhances the adrenal release of aldosterone.
The result is profound angiotensin-mediated vasoconstriction and aldosterone-induced sodium and water

retention, causing renovascular hypertension. Selective renal angiography remains the gold standard for the diagnosis of renal artery aneurysm. However, because of the invasive nature of the procedure, various non-invasive imaging modalities have been applied to detect renal artery aneurysm and stenosis including Doppler ultrasound, MR angiography and CT angiography. Duplex ultrasound can provide images of the renal arteries and assess blood-flow velocity and pressure waveforms, however there is a 10% to 20% rate of failure due to the presence of obesity or bowel gas, respiratory renal movements, and poor patient compliance. At present the most important role of ultrasonography is its apparent ability to predict functional recovery based on the measurement of resistive index. Multidetector CT angiography is the most widely used scan in the diagnosis of aneurysm and renal artery stenosis. It permits rapid volumetric acquisition with high-contrast enhancement of the vessel lumen. Due to the high spatial resolution it provides excellent visualization of the renal arteries as well as side branches. The study conducted by *Sabharwal et al.* (10) reported a 100% diagnostic accuracy of CT angiography in the detection of renal fibromuscular dysplasia and its complications (stenosis, aneurysm). Various surgical techniques for treating renal artery aneurysm have been described (11). Operations included in situ aneurysmectomy and angioplastic renal artery closure or segmental renal artery reimplantation, aneurysmectomy and renal artery bypass, and planned nephrectomy for unreconstructable renal arteries or advanced parenchymal disease. Endovascular therapy has a role in the treatment of distal renal artery branch aneurysms by embolization. The most important indication for surgical repair appears to be the presence of concurrent hypertension and female gender because rupture has been associated with a high death rate, especially during pregnancy (12), with size a relative but secondary consideration.

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CASE REPORT

Headache: A unique clinical presentation for renal cell carcinoma (RCC).

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Summary

Brain metastases of renal cell carcinoma (RCC) are generally seen in advanced stages of disease with a short life-expectancy. A solitary, synchronous brain metastasis of RCC is rare and neurological symptoms may be the presenting sign of cancer. An aggressive surgical approach is justified in patients with favorable prognostic factors (good performance status, age under 65 years, absence of extracraneal lesions) for palliation of symptoms and improvement of cancer-related survival.

KEY WORDS: *Renal cell carcinoma; Metastasis; Brain.*

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INTRODUCTION

Renal cell carcinoma (RCC) has a great metastatic potential; nearly one fourth of patients have metastases at presentation while another 25% develop metastases within 5 years of nephrectomy. Besides the most common sites of metastasis- lung, bones, liver and adrenal glands- RCC metastasises to different brain regions in 5% to 10% of cases (1).
In most cases, brain metastases are seen in advanced stages of the disease, usually with evidence of widespread disease and a short survival time.
A single, metachronous brain metastasis of RCC may be seen many years after the definitive treatment of the primary tumour.
A synchronous solitary brain metastasis is exceedingly rare and, to the best of our knowledge, only *Thyavihally et al.* (2) reported one case among 13 patients with synchronous RCC metastases.
Here we present a case in which a persistent headache was the inaugural sign of RCC.

CASE REPORT

A 62-year-old man was admitted to our hospital with a history of dull, persistent headache of 2 months duration. At physical examination, there were no other neu-

Figure 1A-C.

Brain CT (A) and MRI (B): a 3 cm in size mass is visible in the right temporal region. On abdominal CT (C) a 7 cm solid tumour was found in the right kidney.

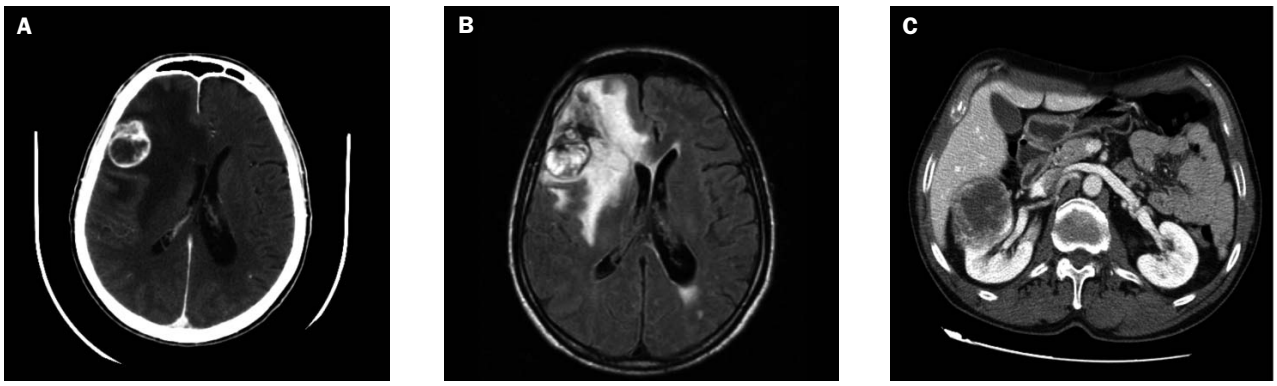
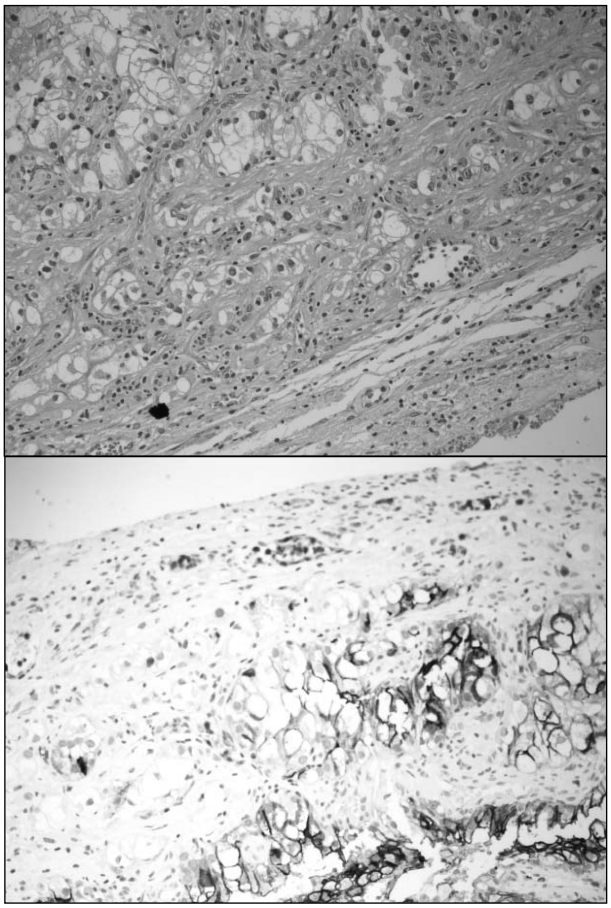


Figure 2.
Metastasis from RCC: nodular proliferation of polygonal clear cells with round nuclei, arranged in short strings, are delimited by neural tissue (bottom right) H&E 125x. Inset: Cytoplasmatic membranes of clear cells show a strong himmunohistochemistry positivity to CD10, Vimentin and cytocheratin 7.250x.



rological signs or symptoms. The patient underwent a brain CT with contrast medium (Figure 1A) that revealed a solid, 3 cm in size mass in the right temporal region with a pronounced enhancement effect; this finding was confirmed by an MRI (Figure 1B). Excision of the mass was performed in the Neurosurgery Department and histologic examination of the surgical specimen revealed metastasis from a RCC (Figure 2). An abdominal CT showed a 7 cm solid tumour in the right kidney (Figure 1C) and the patient underwent a radical nephrectomy. The definitive pathological diagnosis was clear cell renal carcinoma Fuhrman grade II; pT3a M1.
Postoperative course was uneventful and the patient was discharged on 5 day p.o. No adjuvant systemic therapy was carried out; at 6 months follow up, there is no evidence of distant metastases and the patient is asymptomatic.

Discussion

The prognosis of metastatic RCC is generally poor: the average survival is about 4 months and only 10% of the patients survive for 1 year (2).
However, there is a small subset of patients with a solitary metastasis from RCC, in which surgery (radical nephrectomy plus metastasectomy) offers a chance of survival with limited morbidity (3). In these patients, the 5-year overall survival ranges from 20% to 30% (2, 3).
The best outcome was observed in those with metachronous tumours appearing more than 1 year after nephrectomy (median overall survival 55 months vs 33 months if metastasis occurred before 1 year after surgery), with low primary tumor stage and grade and those with bone and pulmonary parenchymal metastasis. Patients whit metachronous lesions fared better than those with a synchronous metastasis (5-year survival rates of 39% and 22%, respectively) regardless of the metastasis site (3).
For patients with brain RCC metastasis, the following factors are associated with the best outcome (4-6):

1) metachronous brain metastases more than 1 year after nephrectomy;
2) good patient performance (Karnofsky > 70);
3) patient's age under 65 years at the time of initial diagnosis;
4) solitary metastasis with a diameter < 2 cm;
5) minimal or no neurological deficit;
6) no systemic symptoms (fever, weight loss);
7) absence of/or minimal extracranial metastases at the time of craniotomy;
8) location of the brain metastasis (in relation to the completeness of resection).

Brain metastases tend to be well-circumscribed with a surrounding pseudocapsule and can often be removed with surgical resection or stereotactic radiosurgery (SRS). Surgical resection is preferred when a pathologic diagnosis is needed, for tumors larger than 3.5 cm or when immediate tumor mass decompression is required; SRS should be applied for single tumors less than 3.5 cm in surgically inaccessible areas and for patients who are not surgical candidates (8).
Surgical resection of a solitary brain metastasis frequently provides immediate and prolonged improvement in neurological symptoms and is effective in the prolongation of life.
Swanson (3) reviewed the literature and concluded that the disease-free and overall survival rates were 20% and 18%, respectively. *Wronski et al.* (9) reported a survival time from craniotomy of 12.6 month in a series of 50 patients with RCC brain metastases; *Pomer et al.* (5) reported a 1-year survival rate of 31% for patients treated by surgical resection vs. 15% for those treated by radiotherapy, respectively. In their experience, brain metastasectomy yields an additional median survival advantage of 8 months as compared to untreated patients.
In Harada's series (18 brain metastasis out of 325 cases with RCC) the 1-year survival rate after the diagnosis of brain metastasis was 43.2% (64.8% in surgical treated group, 0% in nonsurgical group) and the 3 and 5-year survival rates were 18.5% and 0% (10). The published results do not support the routine use of adjuvant systemic therapy after resection of a solitary meta (3). Chemotherapy has been demonstrated to improve response rates when used as an adjunct to radiation therapy; however, these improvements in response rates have

not been correlated with an improvement in median survival (8).

In selected patients with a solitary brain metastasis from RCC, radical nephrectomy plus metastasectomy is recommended for palliation and survival prolongation. The actual outcome depends on multiple factors (patient's performance status and age, location of metastasis, disease free interval before development of metastasis, low primary tumor stage and grade.

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ORIGINAL PAPER

First Italian experience in single incision laparoscopic nephrectomy. Assessing and overcoming new challenges.

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Summary

Background: *The need to enlarge one of laparoscopic holes for specimen retrieval at the end of a laparoscopic nephrectomy, suggested us to use this final access for the entire procedure. We describe our technique placing trocars directly on the fascia once the skin and the subcutaneous layers were prepared.*

Material and methods: *A 10 consecutive patients series operated by Single Incision Laparoscopic Nephrectomy (SILN) is presented. With a 5 cm mean skin incision, the fascia was prepared and 3/4 trocars inserted separately directly on the fascia. Surgical strategy followed the standard technique, except for the use of articulating instruments and 5 mm optic. Demographics, Body Mass Index (BMI), operative time, blood loss, perioperative complications, transfusions, hemoglobin decrease, analgesic requirement, length of stay, final pathology were recorded. Postoperative and prior-to-discharge Video Analogue Scale Pain (VAS) evaluation were also collected, together with the limitations inherent to the instruments placing and parallel driving during the procedure.*

Results: *SILN was successfully completed in all but one cases. The mean operative time was 169 min (mean blood loss 113 ml). Without major perioperative complications, the patients were discharged early (mean 5.3 days). Four patients had a BMI > 30. For specimen retrieval (neoplasms) two trocars holes were joined. One patient required analgesics; the mean post-operative and prior-to-discharge VAS scores were 5.7 and 1.4, respectively. Pathology examination confirmed 4 pyelonephritic kidneys, 4 renal carcinoma and 2 upper-urinary tract carcinoma.*

Conclusion: *SILN is feasible, safe, with favourable perioperative and short-term outcomes. It's technically more challenging than standard laparoscopy requiring advanced surgical skills.*

KEY WORDS: *Urology, Laparoscopy, Nephrectomy.*

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INTRODUCTION

The laparoscopic developments of surgery have led both surgeons and patients to a minimally invasive mindset for the address of surgical diseases. Natural orifice transluminal endoscopic surgery (NOTES), in recent years, has become an experimental issue in surgery (1). The purpose of this technique is to realize surgical operation using natural orifices allowing the operation to proceed without abdominal scars. In urology clinical experience with NOTES is extremely limited (1-4). Nevertheless, the large experience in animal model seems to support the idea that the nephrectomy could represent one of the more appropriate targets, but its performance in humans is challenging (5-8).

In the last years, besides NOTES, Single Incision Laparoscopy Surgery (SILS) has became one of the more interesting surgical techniques (1). SILS uses one abdominal incision to address surgical procedures keeping the advantage of laparoscopy and offering less surgical trauma.

SILS could be performed by the use of new multichannel dedicated trocars (6, 9-11) or standard ones (11-12), the incision being made transumbilically or not (11).

It is also emerging from the literature that SILS could be performed also by using an additional trocar especially for right-sided disease (12) or in cases of complex procedures (8-9), generally to better expose the operatory field. Whereas pure NOTES is still experimental, SILS

procedures are already being clinically implemented (1) and technically feasible for a wide range of interventions (7, 9, 13). Herein, we report our initial experience with pure single incision laparoscopic nephrectomy.

Methods

Patients selection

From July 2008 to March 2009 all patients with indication for a simple or radical nephrectomy, suitable for a minimally invasive approach underwent to SILN at our institution. Our inclusion criteria were: small non-functioning kidney, small (< 4 cm) renal masses not suitable for nephron sparing surgery (central or hilar masses), and renal contrast-enhancing masses < 7 cm. Patient demographics, comorbidities, Body Mass Index (BMI) were recorded. Prior to surgery, all patients undergoing the SILS nephrectomy were informed that the procedure would be attempted via a single incision; all patients gave the consensus to additional incisions if necessary. Stage and grade were assigned following TNM 2002 (14).

Access technique

The patient is placed in the 45-60 degrees modified flank position with the operating table minimally flexed. The surgeon and the assistant stand facing the patient's abdomen. We used a supraumbilical pararectal or transumbilical incision. Deeper layers were retracted until the fascia was clearly exposed. Then, a central first 10 mm trocar was inserted following the Hasson technique and ensured by a single stitch. The pneumoperitoneum was developed (14 mmHg). Therefore, two additional 5 mm trocars were placed at the edges of the prepared fascia (Figure 1).

The only transumbilical approach was achieved with a 3 cm open laparoscopy and developed as described above.

Surgical technique

Enoxaparine 4000 IU subcutaneously was administered the evening before surgery, that continued postoperatively once daily until day 21 postoperatively.

Using a standard 10 mm 30 degrees lens laparoscope (light source insertion at 90°) the peritoneal cavity was examined. The surgical strategy followed the conventional one previously described (15).

The colon, liver/spleen and ureter dissection were done using a combination of articulating, straight surgical instruments and harmonic scalpel (Figure 2). During the approach to the hilum the articulating device was utilized for retraction, whereas straight instruments were preferred for fine preparation of the vessels. At this point

Figure 1.

Step by step access technique.

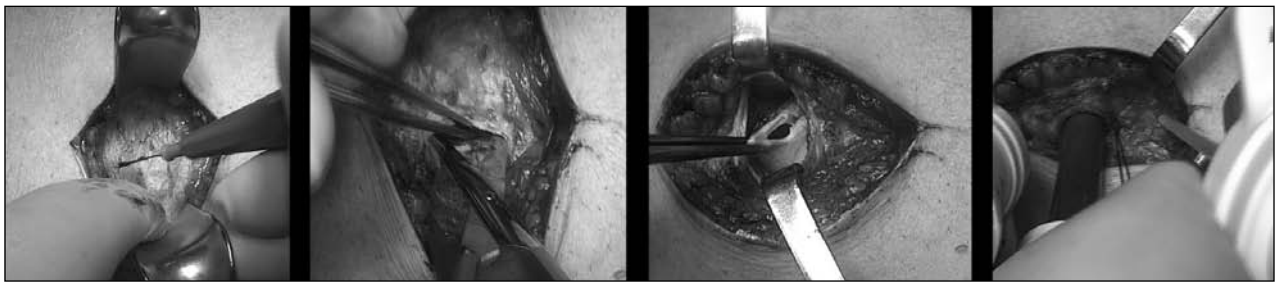
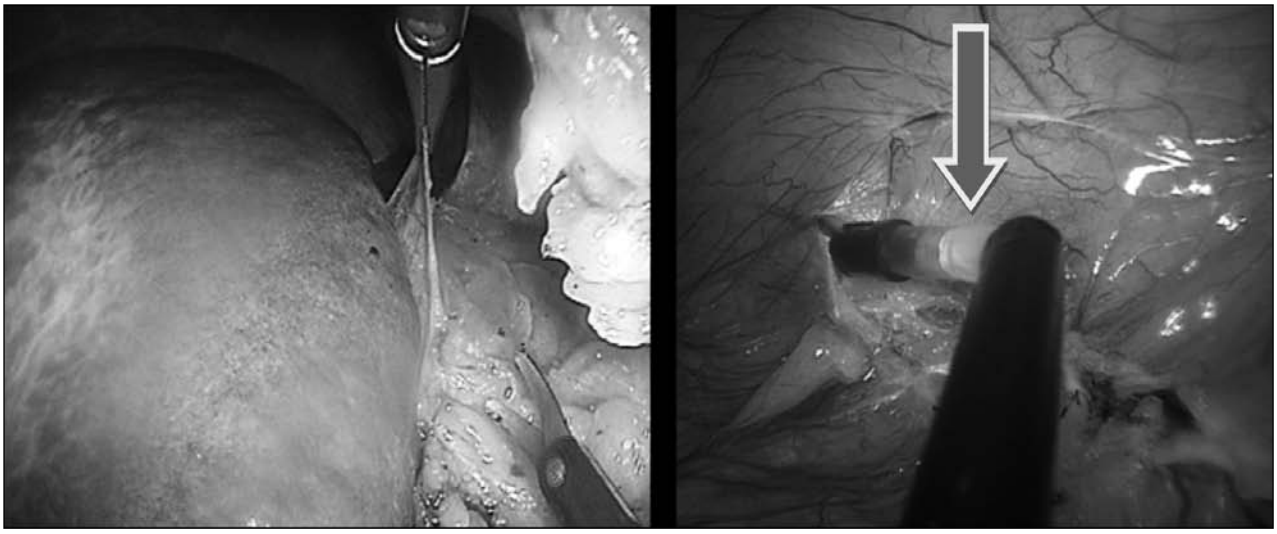


Figure 2.

Intracorporeal operative view of the laparoscopic spleen and colon dissection (note the articulated instrument, grey arrow).



we shift to 5 mm optic in order to use the central 10 mm trocar for the introduction of laparoscopic stapler or 10 mm clip applier (Hemolock).
Then the renal artery and renal vein were subsequently ensured and divided. The remaining attachments were divided by harmonic scalpel. In consideration of the specimens size we use alternatively small (10 mm) or big (15 mm) laparoscopic bag. For the insertion of the big sack, we remove the central trocar and directly inserted in this free hole the bag. For the specimen retrieval we joined two or three trocar holes; whereas no further fascial incision extension was done when not needed. A tubular drain is left in situ through the same fascial and skin access.
Postoperatively, all patients received continuous intravenous ketorolac for 24h as well as intravenous narcotics as needed. Patients were discharged home when they were tolerating a diet and had stable hemoglobin.

Outcomes

ASA class risk, operative time, estimated blood loss, perioperative complications, transfusion requirement, decrease in serum hemoglobin, analgesic requirement, length of stay, size of the skin incision and final pathology were recorded. The Visual Analog Pain Scale (VAPS) (1: negligible pain - 10: severe discomfort/pain) allowed for pain assessment postoperatively (POD1) and prior to discharge (16).
All the limitations inherent to the instruments placing and parallel driving during the procedure were collected at the end of each intervention (e.g. the internal and external collision of the instruments; the handle-related problems; constant gas leakage).

Results

Patients characteristics, indications and final pathological findings are summarized in Table 1. Specifically a total of 3 men and 7 women underwent single incision laparoscopic nephrectomy (mean age: 64.9 y; range 47-83) Nephrectomy was performed in 4 cases for a small non-functioning kidneys (mean longitudinal axis 7.9cm; mean weight 260 grams) and the pathology confirmed the preoperative diagnosis. Four patients underwent to radical nephrectomy for renal contrast-enhancing masses (mean tumor size 5.1 cm, range 3-6; mean longitudinal axis 9.5 cm; mean weight 435 grams). The final pathological report showed 3 clear cell carcinoma (2 pT1b and 1 pT3a) and 1 oncocitoma. Two patients underwent to radical nephroureterectomy for upper urinary tract urothelial carcinoma (mean longitudinal axis 13.5 cm; mean weight 790 grams). The final pathological report confirmed 2 high grade carcinoma (stage pT2 N0 M0 and pT3a N0 M0).
All patients have been operated in the flank position, after urinary catheter insertion. We had one conversion to open surgery for uncontrollable bleeding during ilar approach; and one conversion to conventional laparoscopy for technical problems. The mean skin incision size was 5 cm (range 3-7), specifically, the mean size was 3.7 and 5.8 in simple and radical nephrectomy, respectively. In all cases the fascia preparation and trocars insertion were done without difficulties; a central first 10 mm trocar was always inserted, and two more 5 mm trocars were placed at the edges of the exposed fascia. In 2 cases (BMI > 30), for right nephrectomy, we added a 5mm trocar for liver retraction without supplemental skin incision (Figure 3).

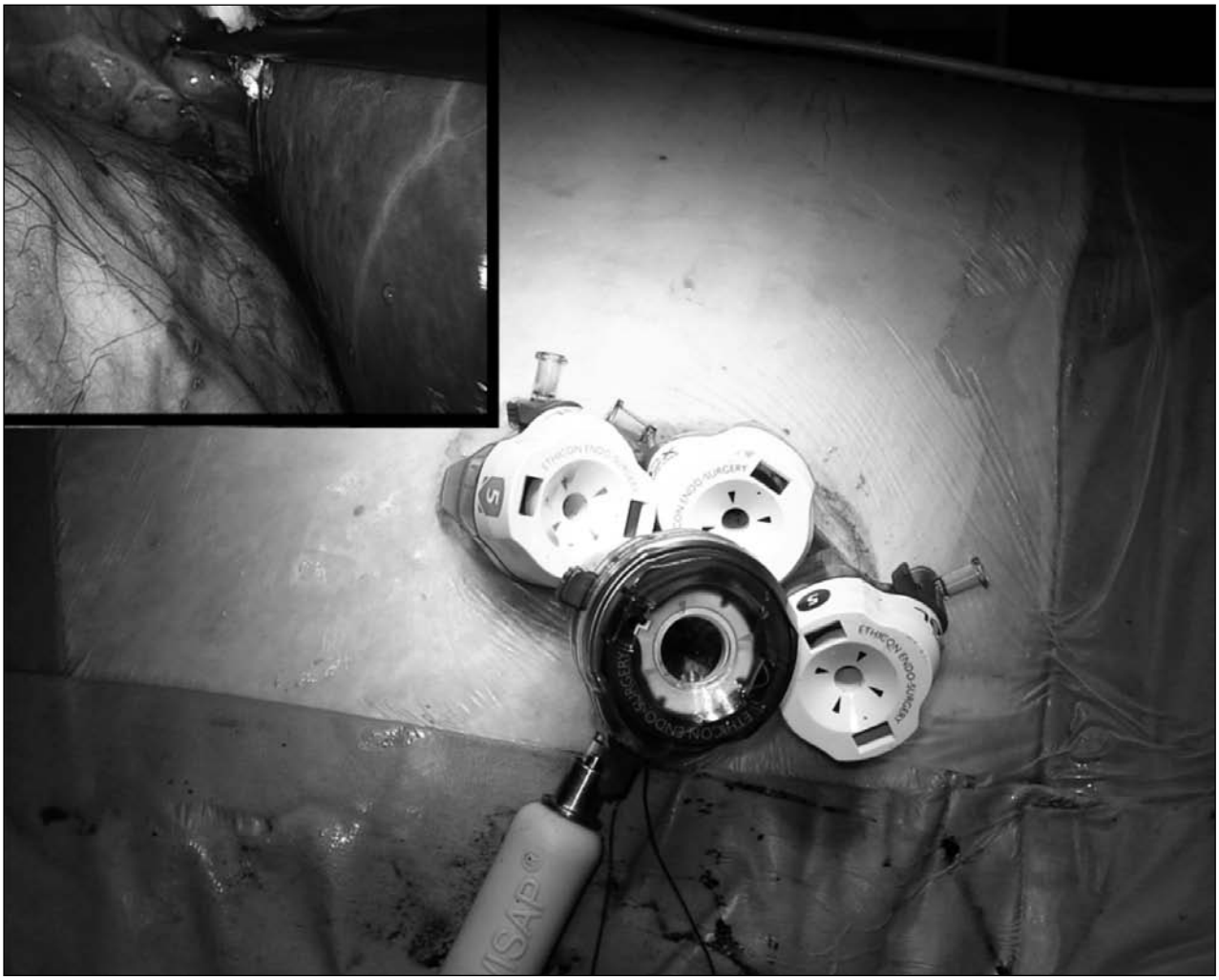
Table 1.

Demographics and perioperative characteristics of patients.

Patient number	Age/side/ gender	Indication/ approach	Comorbidities/ BMI	ASA class risk	Operative time (min)/blood loss (ml)/specimen weight (gr)	Decrease in serum Hb (gr/dl)	Lenght of stay	Number of trocars/ incision (cm)	Articulating instruments	Extraction	Haemostasis	Complication/ transfusion	Pathology longitudinal mean tumor size
1	78/L/M	NFK/par	Hy/25.2	II	180/50/300	1	6	¾	Scissor + gasper	Small endobag	Endogia for vein; Haemolock for artery	No/no	Pielonephritis/9/-
2	76/R/F	RCC/par	Hy/29.2	II	150/300/480	3.7	4	4/7	Scissor	Big endobag	Haemolock for artery and vein	No/no	RCC/11/6
3	52/R/F	TCC/par	-/25.4	II	240/400/830	4.3	7	4/6	-	SILS incision	Haemolock for artery and vein	Conversion to open for bleeding/no	TCC/14//4
4	83/L/F	RCC/par	Hy, COPD/25.7	III	120/20/450	1	7	3/5	-	Big endobag	Haemolock for artery and vein	Ileus/no Conversion to	Onco/10/3 Pielonephritis/8/-
5	70/L/M	NFK/par	Hy, COPD, Di/36.1	III	180/250/290	2.2	7	¾	Scissor	Big endobag	Haemolock for artery and vein	standard VLP for aderences/no	
6	47/L/F	RCC/par	Hy/30.5	II	210/20/360	0.5	5	3/5	.	Big endobag	Haemolock for artery and vein	No/no	RCC/10/6
7	51/R/F	NFK/hu	-/19.1	II	120/10/240	0.5	3	3/3	-	Small endobag	Haemolock for artery and vein	No/no	Pielonephritis/7.8/-
8	50/R/M	RCC/par	Hy/27.8	II	180/50/450	1.7	5	3/5	-	Big endobag	Haemolock for artery and vein	No/no	RCC/10/5.5
9	61/L/F	NFK/par	Hy/32	III	150/10/210	0.5	5	3/4	-	Big endobag	Haemolock for artery and vein	Gastritis/no	Pielonephritis/7/-
10	79/R/F	TCC/par	Hy/33.8	III	160/20/750	0.5	4	4/7	-	Big endobag	Haemolock for artery and vein	No/no	TCC/13/2

Figure 3.

Right single incision nephrectomy. Note the forth trocar placed in the same incision for liver retraction, right upper corner.



As far as the accesses is concerned, we performed a supraumbilical pararectal 3 to 7 cm skin incision in all cases but one case, in which we performed a 3 cm transumbilical incision (BMI < 20).
In 3 cases for achieving a satisfying dissection and triangulation we used articulating instruments, in 7 cases the operation proceeded only by the use of standard straight devices.
During the renal artery and vein ligature, the optic was changed, and a 5 mm optic was introduced in a small trocar, then a 10 mm clips applier or 10 mm linear vascular stapler was introduced in the 10 mm trocars: then the 5 mm optic was utilized till the end of the procedures. Only in one case, the small diameter of artery and vein lead us to apply clips through an 5 mm clips applier.
For nonfunctioning kidneys we used 10 mm sack through the main trocar under visual control from the 5 mm optic. In case of radical nephrectomy and nephroureterectomy the kidney was removed intact using the bigger 15 mm bag inserted instead of the 10 mm trocar under visual control. For the final extraction of the kidney the incision holes was joined reaching the exact size for specimen. No enlargement of skin incision was needed.
The postoperative was uneventful without major postoperative complications. One patient had ileus, spontaneously resolved in 4th POD, and 1 patient complaint of gastritis treated by intravenous omeprazole. Only the patient who received an open laparotomy conversion, required analgesic supply in POD 2. The mean VAS was 5.7 ± 1.5 in first POD and 1.4 ± 0.5 prior to discharge. Six patients started oral intake in 1POD, 2 in 2POD, 1 in 3 POD and 1 in 6 POD. The mean time to oral intake was 2 days.
The surgeon's complaints were i) an internal and external collision of the instruments (1/10 and 3/10); ii) severe handle-related problems (hand crossing, rupture of gas connector on the trocar) (1/10); iii) a constant gas leakage (1/10).

Discussion

Attempting to further minimize surgical trauma, single incision accesses to the abdominal cavity have been described in umbilicus (the so called embryonic NOTES

or scarless SILS) or in extraumbilical sites (10). Here we describe our experience and our technique to perform SILN in benign and malignant conditions. After a short skin incision (mean length 5cm) and the preparation of the fascia, we accessed to the peritoneum with the trocars inserted directly into the fascia (17).

Usually, once the specimen is entrapped in the bag, the surgeon have to wide one or join more than one trocar holes for the extraction of the kidney, often resulting in a "final incision" added to the initial trocar incisions. We tried to further minimize the number and the total length of the incisions, thinking at this "*final incision*" and exploiting it to perform the entire procedure from the beginning. In this way the final amount of muscle-fascial trauma was minimized during the operation (less centimetres and less traction) and no "*final incision*" was needed for the kidney retrieval. Regarding access location, we performed a supraumbilical pararectal ipsilateral skin incision in all cases but one, in which we preferred a 3 cm transumbilical incision (female, BMI 19). The choice of the access could be oriented by the anthropometrics of the patient. When the distance between umbilicus and kidney is appropriate for instruments length a transumbilical incision should be adopted, whereas the SILS allowed us to operate corpulent patients (5 BMI 25-30, overweight; and 4 BMI > 30, obese) without instruments length related problems (9). In all cases, the single incision was sufficient to retrieve the specimen. The mean skin incision size was 3.7 vs 5.8 cm in simple and radical nephrectomy, respectively, and it was probably related to the difference in mean specimen size between non functioning and malignant kidney (7.9 vs 10.5 cm). These data confirm that the final length of the incision largely depends on the volume of the kidney. Right laparoscopic nephrectomy even in standard laparoscopy, frequently imposes the use of an additional instrument for liver retraction. In the present series we needed a supplemental port for liver retraction in 3/5 cases (2 TCC and 1 RCC). The pararectal single incision was sufficient to add a fourth 5 mm trocar for the liver retraction, even increasing the external clashing of the instruments.

In 3 cases for achieving an optimal dissection and triangulation we required articulating instruments, while in 7 cases the operation proceeded only by the use of standard straight devices. The vessel control had be addressed by 10 mm Hem-o-lock clip or 10 mm linear vascular stapler (first case). As described in methods, we shifted to a 5mm optic, placed in a small trocar, in order to set free the 10 mm port for the vessel synthesis devices.

Following this strategy all but two the procedures were entirely completed by SILN. Specifically, the first case of conversion to open surgery was related to a unexpected and uncontrolled hilar bleeding in a patient with a caliceal pT3a G3 TCC (Table 1). The bleeding was promptly repaired and the nephroureterectomy was completed by the single incision. The second conversion (to standard laparoscopy) was due to the presence of widely-spread adherences in a obese (BMI 36) patient with chronic pyelonephritis. The common postoperative outcome indexes suggested a prompt recovery of bowel function, a painless mobilization and an early discharge.

The present study has such limitations. The 10 cases represented a limited sample to allow robust conclusions, nevertheless they represent only our ongoing experience in developing SILS nephrectomy (17). On the other side, we describe only a prospective series without a control arm (e.g. standard laparoscopy). This latter point hinds any comparison between intraoperative and postoperative outcomes limiting the power of our conclusion. *Raman et al.* published the only one match-paired (2:1) study and concluded that there were no differences between standard and SIL nephrectomy (18) in terms of common intraoperative and postoperative parameters. Comparing their and our series we cannot find great differences in demographics and surgical outcomes (18). This similarity underscores how this new approach could be considered feasible and safe not only in the hands of an experienced and world-recognized laparoscopic surgeons, but also in urologists who had completed the traditional laparoscopic learning curve.

We recognize that the absence of clear advantages of SILN over standard laparoscopy is one of the most robust argument in favour of the greatest benefit in cosmesis. Although the prevalence of female population in Raman and present series well support this idea (18). Anyway, this is only a preliminary study, that should be confirmed by larger studies on humans with a adequate power in order to detect a significant differences in outcomes. Finally, as operative SILN experience increases, we expect a greater technological implementation by the industry about devices (cameras and instruments).

Conclusions

Even if our experience is at the beginning, we demonstrated the feasibility of SILS for benign and malignant kidney diseases. The SILN is an extirpative surgery that require for the intact specimen retrieval no more than the "*final incision*" used in standard laparoscopy. It should be one of the third-generation laparoscopic procedures easy to teach and to learn, although NOTES still in an experimental setting. Prospective and comparative studies are required to demonstrate the superiority or equivalence of this technique in comparison with the standard laparoscopic nephrectomy.

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CASE REPORT

Retrograde ejaculation and abnormal hormonal profile in a subject under treatment with valproate and phenytoin.

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Summary

Anti-epileptic drugs may have negative effects on sexual function and hormonal profile. The exact mechanisms involved, however, have yet to be completely understood. We report a case of ejaculation failure and abnormal hormonal profile in a patient affected by epilepsy. A 59-year-old man, under treatment with valproate and phenytoin for 15 years, complained of orgasmic anejaculation over the previous 6 months. He was not affected by other relevant pathologies and he had not undergone pelvic surgery. We found spermatozoa in post-orgasmic urine, which confirmed our suspicion of retrograde ejaculation. The hormonal profile showed high levels of FSH, LH and, surprisingly, increased levels of total testosterone and SHBG. We hypothesized bladder sphincter inhibition and receptor alterations due to the anti-epileptic drugs.

KEY WORDS: Valproate; Phenytoin; Retrograde ejaculation; Sexual function; Anti-epileptic drugs.

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INTRODUCTION

In recent years, we have observed a reduction in male fertility; among the factors that could affect semen parameters, therapeutic drugs also play a role. Anti-epileptic drugs, in particular, may act negatively on endocrine testicular function. In fact, in certain cases, men affected by epilepsy have been shown to suffer from subfertility and sexual dysfunction (1); however, to date, there is little information on how anti-epileptic drugs can influence these two functions. In particular, few cases of ejaculation failure have been studied. We report a case of retrograde ejaculation and hormonal profile alteration in an epileptic subject treated with valproate and phenytoin.

CASE REPORT

A 59-year-old man attending our Andrology Unit complained of orgasmic anejaculation for the preceding six months. He reported having normal sexual desire and erectile function.

He had been taking anti-epileptic drugs in polytherapy with valproate (daily dose 500 mg) and phenytoin (daily dose 100 mg) for the previous 15 years, as he was suffering from epilepsy.

His medical history showed natural delivery, normal psychological and physical development; he was married and had two sons.

He had not undergone any pelvic, prostate,urinary or bladder surgery and he was not affected by metabolic, hepatic or neurological pathologies apart from epilepsy.

At clinical examination, the subject was phenotypically normal, with a normal piliferous system, normal distribution of panniculus adiposous (BMI = 24) and he did not present gynecomasty.

The hormonal profile showed increased levels of FSH, LH and, surprisingly, total testosterone and SHBG were also elevated. Prolactin, FT3, FT4, TSH and E2 were in the normal range. The hormonal profile was confirmed by three examinations (basal, after 30 and 60 days) and the reported values represent the mean. PSA was also in the normal range (Table 1).

Ultrasound (US) examination showed normal structure and size of the testes (right testicle: 20.3 ml; left testicle: 19.7 ml). In particular, no focal pattern for Leydigioma

Table 1.
Hormonal profile, SHBG and PSA. The reported values represent the mean of three examinations.

	Mean values	Normal range
FSH	31.4 ± 7.5	1.0-8.0 mIU/ml
LH	15.9 ± 2.8	2.0-12.0 mIU/ml
Testosterone	10.4 ± 1.4	2.8-8.0 ng/ml
Prolactin	8.4 ± 2.6	1.6-18.8 ng/ml
TSH	1.32 ± 0.79	0.35-4.00 uIU/ml
FT3	2.91 ± 0.23	2.50-3.90 pg/ml
FT4	0.97 ± 0.17	0.6-1.15 ng/ml
E_2	24.3 ± 1.5	20.0-56.0 pg/ml
SHBG	79.8 ± 10.0	13.0-71.0 nmol/l
PSA	1.2 ± 0.3	< 4.0 ng/ml

was observed; the epididymis and deferent ducts were also normal. Furthermore, the prostate, seminal vesicles and penis US showed no alterations.
Cranial MR with contrast-enhancement excluded pituitary disease.
The presence of spermatozoa in post-orgasmic urine (3-4 spermatozoa in each pellet of 6 urine aliquot of 10 ml) confirmed our suspicion of retrograde ejaculation.
To better correlate this clinical picture with antiepileptic drugs, we now need to request his neurologist to either stop or switch therapy for his epilepsy.

Discussion

This report considers two particular aspects of this patient's condition; retrograde ejaculation and abnormal hormonal profile in a subject suffering from localization-related epilepsy and treated with polytherapy (valproate and phenytoin) for 15 years.

Regarding the first aspect, in the literature there are few reports on the ejaculation mechanism and anti-epileptic drug therapy.
Leris et al. (2) and *Labbate et al.* (3), reported two cases of ejaculatory failure and complete and/or incomplete anorgasmia in men treated respectively with carbamazepine and gabapentin.
In the case here reported, we found a condition of retrograde ejaculation; this is in disagreement with the previous authors, who had excluded this condition.
We hypothesize that, in our case, polytherapy could have acted on the bladder sphincter, inhibiting its closure during ejaculation.
The second aspect regards the hormonal profile; we found elevated levels of FSH and LH as well as a surprising increase in testosterone and SHBG. This is in total disagreement with *Isojarvi JI et al.* (4) and *Herzog AG et al.* (5). Since diagnostic procedures excluded pituitary and testes tumors, we believe that, in the case here reported, pituitary and/or testicular receptor alterations may be implicated.
In conclusion, this report suggests a possible relationship between anti-epileptic drug polytherapy (valproate and phenytoin) and both retrograde ejaculation and hormonal profile alterations. Further research is required to better define the mechanisms involved.

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CASE REPORT

Alfuzosin induced thrombocytopenia after treatment for benign prostatic hyperplasia.

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Summary

We report on 1 case of alfuzosin induced thrombocytopenia after treatment for benign prostatic hyperplasia. This side effect has been recognized 3 months after the alfuzosin treatment. The diagnosis was made by complete blood count (CBC). Peripheral blood smear of the patient was referred to an hematologist to exclude pseudothrombocytopenia and review of the peripheral smear confirmed the decreased platelets with no clumping. Manual count of platelets was similar to the result of complete blood count. After cessation of alfuzosin treatment thrombocytopenia improved and thrombocyte count reached to normal on week 2 following the discontinuation of treatment. Recovery of thrombocytopenia after discontinuation of alfuzosin treatment and recurrent depletion of platelet count after initiation of alfuzosin, supports our thoughts about drug-induced thrombocytopenia (DITP) caused by alfuzosin. The patient was prescribed different alfa blocker and he faced no problem.

KEY WORDS: *Alfuzosin; Benign prostatic hyperplasia; Lower urinary tract; Thrombocytopenia.*

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INTRODUCTION

Voiding dysfunction is common among elderly men and typically involves several lower urinary tract symptoms (LUTS) including voiding/obstructive symptoms such as weak stream, the feeling of incomplete emptying, hesitancy and intermittency as well as storage/irritative symptoms such as frequency, urgency, and nocturia.

Typically, the presence of male voiding dysfunction has been attributed to the presence of benign prostatic hyperplasia (BPH). This has been based upon a pathophysiological model in which the histologically diagnosed BPH leads to prostatic enlargement, which in turn causes bladder outlet obstruction (BOO). In this model, contraction of prostatic smooth muscle via α1-adrenoceptors may additionally contribute to BOO and hence LUTS. More recent data, however, question whether BPH and/or BOO is indeed the sole or at least major cause of LUTS in elderly males (1, 2).

Based upon such models, the treatment of LUTS suggestive of BPH has been based upon attempts to shrink the prostate either by surgical means (including minimally invasive approaches) and endocrine treatments such as 5 α-reductase inhibitors. Alternatively α1 -adrenoceptor antagonists (α-blockers) have been used with the idea that they alleviate LUTS by reducing prostatic smooth muscle tone. Over the past decade, α- blockers have become the mostly widely used rational therapeutic approach for LUTS suggestive of BPH (3).

Internationally, these include the quinazolines alfuzosin, doxazosin, and terazosin and the non-quinazolines tamsulosin and, most recently, silodosin.

By inhibiting smooth muscle α1-adrenergic receptors, α1-blockers (i.e., alfuzosin, doxazosin, tamsulosin, and terazosin) relax prostatic and bladder neck smooth muscle and partially relieve LUTS by improving bladder outlet obstruction. These medications have a rapid onset of action (within a few days for improving LUTS) and are considered the most effective monotherapy for the relief of LUTS, irrespective of prostate size. The main side effects associated with α1-blockers are orthostatic hypertension, dizziness, headache, asthenia, rhinitis, and ejaculatory dysfunction (EjD). Rare instances of hypersensitivity, priapism, palpitations, and edema also have been reported (4).

As far as we know, thrombocytopenia formation after alfuzosin treatment for benign prostatic hyperplasia, has not been reported in literature until now. In this article, a case with thrombocytopenia formation secondary to alfuzosin treatment is presented.

Case report

Clinical evaluation revealed benign prostatic hyperplasia (BPH) in a 65 years old male with prostate volume, International Prostate Symptom Score (IPSS), postvoid residual volume (PVR), prostate specific antigen (PSA) and Qmax of 50cc, 18, 100 cc, 2.1 ng/ml and 11 ml/s, respectively. The patient has been prescribed alfuzosin 10 mg once daily for the medical treatment of BPH. Complete blood count (CBC) revealed thrombocytopenia with platelet count 83.000/µl (the normal range is 156.000-373.000/µl) when the patient was on alfuzosin treatment on month 3.

Peripheral blood smear of the patient was referred to an hematologist to exclude pseudothrombocytopenia and review of the peripheral smear of an ethylenediaminetetraacetic-acid blood sample confirmed the decreased platelet count with no clumping.

Manual count of platelets was similar to the result of complete blood count.

The patient's platelet count was noted to be 61.000/µl on month 6. Before initiation of alfuzosin treatment his platelet count was 228.000/µl. His platelet count was gradually recovered to normal value after the discontinuation of alfuzosin.

The patient's platelet count was 148.000/µl in the 2nd week and 243.000/µl in the 1st month after discontinuation of alfuzosin. After 2 month interval, he again used alfuzosin out of his urologist order, as the patient was very satisfied with alfuzosin for his LUTS and platelet count dropped to 80.000/µl. Throughout this period, the patient remained hemodynamically stable and did not show any evidence of bleeding. Other biochemical parameters were within normal ranges.

The patient did not have any other concomitant diseases including viral infections and was not using any other drugs or herbal products. We related the thrombocytopenia with side effect of alfuzosin and ceased the treatment. After prescribing different alfa blocker, platelet count increased gradually and become 150.000/µl on week 2.

Discussion

For the treatment of BPH/LUTS in the United States today, alfuzosin, doxazosin, terazosin, and tamsulosin are the most prescribed a1AR (alpha1-adrenoceptors) antagonists. Terazosin, doxazosin and alfuzosin are non-subtype selective in that they block all three a1AR subtypes (5).

Clinical trials show that the once daily formulation maintains efficacy comparable to that seen with immediate release alfuzosin and significant improvements in urinary flow rate, symptom relief and quality of life may be maintained with up to 1 year of continued use (6-8). Pooled analysis of the results of the 3 randomized clinical trials confirmed statistically significant improvements in peak flow rates, International Prostate Symptom Scores and quality of life, as assessed by the bother score of the International Prostate Symptom Score (6).

The most frequently reported side effects experienced by patients treated with alfuzosin have been dizziness, asthenia and fatigue, occurring in 1% to 7% receiving 10 mg alfuzosin once daily in short-term clinical trials (9). Cardiovascular side effects in patients receiving 10 mg alfuzosin once daily, including blood pressure changes, were not more frequent than in those receiving placebo in pivotal trials (6, 7). Retrograde ejaculation or other ejaculatory disorders were seen in less than 1% of patients on the prolonged release formulation of alfuzosin (9).

In spite of the fact that various complications have been reported, as far as we know, our case is the first to report thrombocytopenia after alfuzosin treatment for BPH. We recognized thrombocytopenia on month 3. After prescribing different alfa blocker, platelet count increased gradually and become 150.000/µl on week 2.

We think that the possible etiological factor for thrombocytopenia was drug-induced thrombocytopenia (DITP). Most cases of drug-induced thrombocytopenia (DITP) are caused by drug-dependent antibodies that are specific for the drug structure and bind tightly to platelets by their Fab regions but only in the presence of the drug.

Typically, DITP occurs 1 to 2 weeks after beginning a new drug or suddenly after a single dose when a drug has previously been taken intermittently. Recovery from DITP usually begins within 1 to 2 days of stopping the drug and is typically complete within a week. Drug dependent antibodies can persist for many years; therefore, it is important that the drug etiology be confirmed and the drug be avoided thereafter (10).

In our case, recovery of thrombocytopenia after discontinuation of alfuzosin treatment and recurrent depletion of platelet count after initiation of alfuzosin, supports our thoughts about DITP caused by alfuzosin. Additional awareness of alfuzosin -induced thrombocytopenia is needed and specific antibody to platelet surface glycoproteins caused by alfuzosin should be further studied to confirm the association.

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CASE REPORT

Open intervascular nephron-sparing surgery for pyelocaliceal transitional cell carcinoma in solitary kidney planned with contrast-enhanced multidetector CT.

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Summary

A 69-year-old man presented with a tumor involving the right renal pelvis and the middle and lower calyces in a solitary kidney.
The patient was determined to preserve left renal function. Intervascular nephron-sparing surgery (NSS) was planned. A contrast-enhanced multidetector computed tomography (MDCT) was performed, providing 3-D reconstructions of the renal artery and collecting system in regard to the tumor. Two trunks of the anterior branch of the renal artery directed to the lower and middle parenchymal segments were identified.
After dissection of the renal vessels, the anterior branch of the renal artery was identified. The trunks directed to the middle and lower segments were ligated and sected, producing an ischemic area. In cold ischemia, the renal pelvis and the middle and lower segments and calyces were ablated. An anastomosis between the ureter and the upper calyx was performed.
Thirty days after surgery, serum creatinine was 3 mg/dl.

KEY WORDS: *Kidney; Kidney pelvis; Renal artery; Carcinoma, transitional cell; Tomography, spiral computed.*

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List of abbreviations

NSS: Nephron-Sparing Surgery;
MDCT: Multi-Detector Computed Tomography;
TCC: Transitional Cell Carcinoma;
TURB: Trans-Urethral Resection of Bladder;
CIS: Carcinoma In Situ.
VR: Volume Rendering;
WHO: World Health Organization.

INTRODUCTION

In 1954, Graves, studying polyester resin casts of cadaver kidneys (1), illustrated the patterns of the renal artery and its branches, in relation to the venous tree and the collecting system. Graves showed that, in most cases, the distribution of the arteries to the kidney follows consistent patterns. His studies were followed and broadened by those of other authors (2), who developed the intervascular intrarenal approach for nephron-sparing surgery (NSS). The increase of incidental finding of renal tumors at smaller sizes and the long-term consequences of radical nephrectomy in terms of deterioration of renal function (3), cardiovascular morbidity, hospitalization and death contributed to develop the interest in NSS.
NSS has been performed in open (4), laparoscopic (5) and robot-assisted laparoscopic surgery (6) with satisfying results in terms of negative margins, and oncologi-

Table 1.
Scanning parameters.

SCAN PARAMETERS	
• Tube voltage 135 kVp. • Current 400 mAs. • Slice collimation 1 mm. • Tube rotation speed: 500 ms.	• Pitch: 1 mm. • Image reconstruction: 0.8 mm. • Scan direction: craniocaudal.
MDCT ANGIOGRAPHY	**MDCT ANGIO-UROGRAPHY**
Patient, lying supine, was studied in the arterial phase with the injection in an antecubital vein of 90 ml of iodinated contrast medium (Iopamidolo(R) 370 mg/ml; Bracco, Italy) followed by 50 ml of saline solution, using a 17G cannula needle and 3.5 ml/s flow by means of a dual head injector (Stellant(TM); Medrad(R), USA). The scanned images were acquired about 25 seconds after the beginning of the intravenous infusion, once 100 HU were reached at the lumen of the abdominal aorta above the origin of the celiac trunk (bolus tracking technique (9)). Patients was instructed to hold his breath for about 10-15 seconds, while scans were being taken from 2 cm above the plane passing from the upper pole of the left kidney to 2 cm beyond the plane passing from the lower pole of the right kidney.	After the portal phase, patients was positioned prone and was given a second intravenous injection of 50 ml of iodinated contrast medium (Iopamidolo(R) 370 mg/ml; Bracco, Italy) followed by 50 ml of saline solution, again with a flow of 3.5 ml/s, by means of a dual head injector (Stellant(TM); Medrad(R), USA). Scanning took place about 12 minutes after beginning of the first intravenous injection: this corresponds to when a level of +100 HU was reached above that measurable at the lumen of the abdominal aorta of the patient, below the origin of the superior mesenteric artery (bolus tracking technique).

cal and renal functional outcomes. While NSS for esophytic masses has become a standard procedure, approach to hilar tumors remains challenging (7), and has been described almost only for parenchymal tumors such as clear cell carcinoma, oncocytoma and angiomyolipoma (7).
NSS must be preceded by a contrast-enhanced multidetector computed tomography (MDCT), which provides 3-D reconstructions of the renal artery or arteries and of the collecting system in regard to the tumor (8).

Case report

A 69-year-old man presented with a recurrence of bladder transitional cell carcinoma (TCC) and a tumor involving the right renal pelvis and the middle and lower calyces. When he was 18 he underwent left nephrectomy for renal tuberculosis. In the recent past he underwent several trans-urethral resections of bladder (TURB) for TCC. The pyelocaliceal tumor was detected while performing a contrast-enhanced CT of the abdomen during follow-up.
The patient, who was in good general condition, was strongly determined to preserve left renal function (serum creatinine was 1,49 mg/dl), and so NSS was planned.
First the patient underwent a contrast-enhanced MDCT.
The patient, lying supine, was studied in the arterial phase with the injection of 90 ml of iodinated contrast medium followed by 50 ml of saline solution. After the portal phase, the patient was positioned prone and was given a second intravenous injection of 50 ml of iodinated contrast medium followed by 50 ml of saline solution. Scanning details are reported in Table 1.
The densitometric data were processed on a Vitrea-Workstation (TM) (Vital-Images(R); USA), obtaining volume rendering (VR) tridimensional reconstructions of the kidney, the renal artery, the segmental arteries, the urinary tract and the tumor. CT showed on the right kidney a large simple cyst on the upper pole, a tumor involving the renal pelvis and the middle and lower calyces, and an ischemic area of unknown origin between the middle and the lower renal segment (Figure 1).
Angiographic 3-D reconstructions allowed to identify the anterior branch of the renal artery and its middle and lower trunks directed to the middle and lower renal seg-

Figure 1.
MDCT, coronal projection. On the right kidney can be observed: a large simple cyst on the upper pole; a tumor involving the renal pelvis and the middle and lower calyces; an ischemic area of unknown origin between the middle and the lower renal segment.

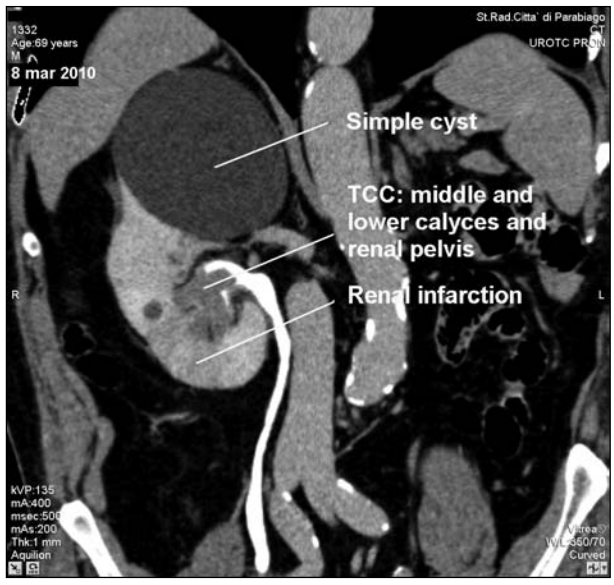


Figure 2.

MDCT, 3-D reconstructions of the kidney, the arterial arteries and the collecting system. Yellow line number 1 marks the trunk of the anterior branch of the renal artery directed to the lower parenchymal segment, which will be ligated and sected. Yellow line number 2 marks the trunk of the anterior branch of the renal artery directed to the middle parenchymal segment, which will be ligated and sected. Yellow spots mark the ischemic areas which will be produced by ligation of the two arterial trunks. The yellow arrow marks the trunk of the anterior branch of the renal artery directed to the upper parenchymal segment, which will be spared.

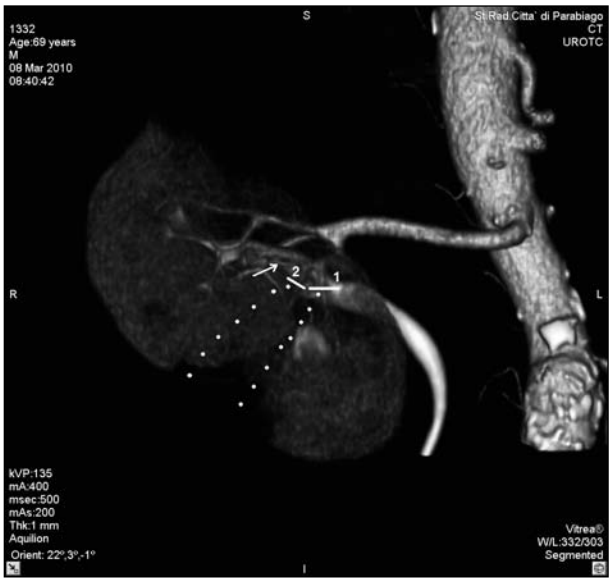
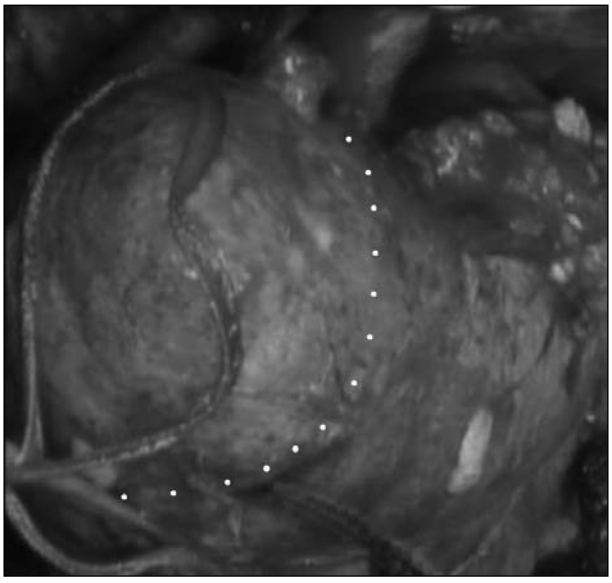


Figure 3.

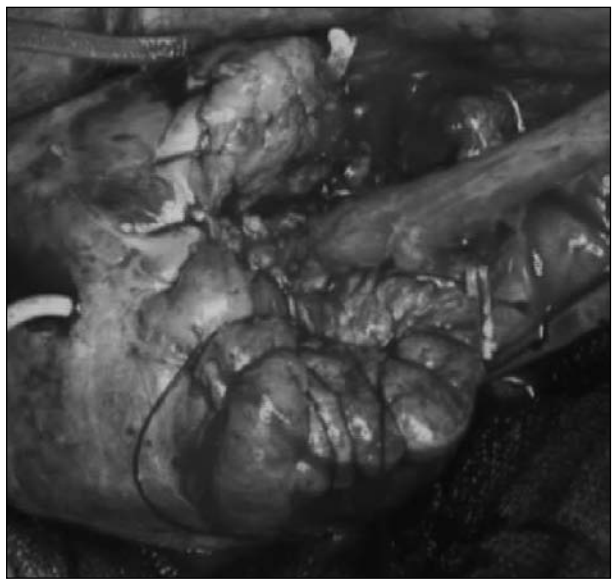
Intraoperative picture. The yellow spots mark the ischemic area produced by the section of the two arterial trunks.



ments, which will be ligated and sected; a branch of the anterior-middle artery directed to the upper renal segment, will be spared (Figure 2).

Figure 4.

Intraoperative picture. The kidney, after ablation of the renal pelvis, the middle and lower parenchymal segments and the middle and lower calyces, and termino-terminal anastomosis between the ureter and the upper calyx.



First a TURB was performed and a ureteral catheter was placed.

The kidney was exposed with a pararectal extraperitoneal access. The large simple cyst was ablated and hilar lymphadenectomy was performed. Careful dissection of the renal vessels was performed toward the renal sinus. The anterior branch of the renal artery was identified.

The two trunks of the anterior branch directed to the middle and lower parenchymal segment were ligated and sected, producing an ischemic area interesting the middle and lower parenchymal segments and the middle and lower calyces (Figure 3).

The trunk of the anterior branch directed to the upper parenchymal segment was spared.

After 15 minutes of cold ischemia with ice slushes, the renal artery was clamped and the renal pelvis, the middle and lower parenchymal segments and the middle and lower calyces were ablated with cold scissors. The renal pelvis resulted to be occupied by a 3 cm neoplasm. Frozen sections of the resection margins resulted to be negative.

After hemostasis and reconstruction of the resection margin, a 8 Fr pig-tail nephrostomy was placed. Finally, a termino-terminal anastomosis between the ureter and the upper calyx was performed (Figure 4).

Total ischemia time was 62 minutes. Blood losses were 600 ml.

Histology showed a bladder carcinoma in situ (CIS); muscular layer was present and unaffected. The pyelocaliceal carcinoma was a high grade TCC according to WHO 2004, affecting the lamina propria. Resection margins resulted to be unaffected.

After surgery there was no need for dialysis treatment, and 30 days after surgery serum creatinine was 3 mg/dl.

Discussion

Approach to hilar tumors is the most challenging in NSS (7), especially in case of TCC, when it is necessary to ablate large parts of the proximal collecting system and then to perform a reconstruction of the urinary tract. Thus, an accurate pre-operative planning is mandatory.
Contrast-enhanced MDCT with VR reconstructions provides surgeons with knowledge of the exact anatomy of the renal arteries and collecting system (8,9). Data obtained with the diagnostic technique used in this case are the result of a virtual sculpting. Results are made possible by targeted, personalized post-processing, using a workstation and specific software for volume rendering in all spatial planes. Diagnostic images are based on the densitometric differences purposely created with strategic space-time use of the contrast medium in the arterial and delayed phase. The arterial phase enables the creation of a clear representation of the arterial tree. MDCT represents the renal artery and its segmental branches (8), identifying the parenchymal vascular segments and the exact position of the avascular areas of the kidney (2). In the delayed phase, the arteries and the urinary tract are simultaneously observed (9), taking advantage of the lower density of the contrast medium in the arteries compared to the higher concentration of the agent in the collecting system.
In order to preserve the integrity of the peritoneum in case of need of dialysis treatment, open extraperitoneal approach was chosen.
Needing a longer ischemia time, we resorted to cold ischemia, obtained by placing sterile ice slushes around the kidney (10).
Selective arterial ligation (2) allowed to create an ischemic area limited to the parenchymal segments interested by the tumor, preserving a part of the kidney sufficient for a satisfying left renal function with no need for dialysis.

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PRESENTATION

Transrectal ultrasound approach for identification and radioguided biopsy of sentinel node in lymph node staging of localized prostate cancer.

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Summary

Introduction: *The limited pelvic lymphadenectomy (LPL) is currently considered the preferred method of identification of nodal micrometastases in localized prostate cancer. Lymphoscintigraphy (LS) and radioguided sentinel node biopsy (RSNB) could be an alternative method of nodal staging.*

Materials and Methods: *Between June 2003 and February 2007 19 patients with prostate cancer without metastases were included in the study. Mean age was 66 years, mean PSA 15.51 ng/ml, Gleason score > 6.*

A transrectal ultrasound was performed with intraprostatic administration of 0.2 ml/190 MBq 99 mTc bound to nanocolloid particles, prepared the day before surgery. Dynamic and static scans of the pelvis were obtained at 30', 60' and 120' after injection. Hot spots outside the site of administration were considered as sentinel nodes (SLNs). Prior to prostatectomy, LPL was performed. The presence of a labeled node after LPL, identified by a gamma probe slided slowly down the chain of lymphatic drainage, was indication for an LPE.

Results: *A sentinel node was identified in 17/19 patients with preoperative lymphoscintigraphy (identification rate 89%) and in 16/19 patients during surgery (84%) with a negative predictive value of 97%. The most frequent site was identified at the level of hypogastric lymph nodes (56%), outside the standard of limited pelvic lymphadenectomy, followed by external iliac (33%), obturator (7%) and common iliac (4%) lymph nodes. Lymph node metastases were detected by histological examination in 2 patients (13%); total metastatic nodes found were 9: one in the first, and 8 in the second patient. Two metastatic nodes (22%) not removed by the limited pelvic lymphadenectomy were found with the sentinel lymph node dissection.*

Conclusions: *Ultrasound approach for lymphoscintigraphy and sentinel node identificatiom, is a valuable tool in the staging of localized prostate cancer.*

KEY WORDS: *Sentinel lymph node; Prostate cancer; Lymphoscintigraphy; Lymphadenectomy; Transrectal ultrasound.*

INTRODUCTION

The limited pelvic lymphadenectomy (LPL) [obturator lymph nodes (LO) and external iliac (EI)] is currently considered the method of choice for regional staging and identification of nodal micrometastases in patients with apparently localized prostate cancer (T1-T2, N0, M0).

Lymph node (LN) metastasis is an unfavourable prognostic factor that influences therapeutic strategies. However, there is no consensus over the extent of pelvic lymph node dissection that is required or the number of lymph nodes that should be removed in order to achieve an adequate staging procedure.

The extended pelvic lymphadenectomy (LPE) shows a high percentage of lymph node metastases outside of the LPL and is associated with a higher frequency of complications. For this, new minimally invasive surgical techniques have been developed.

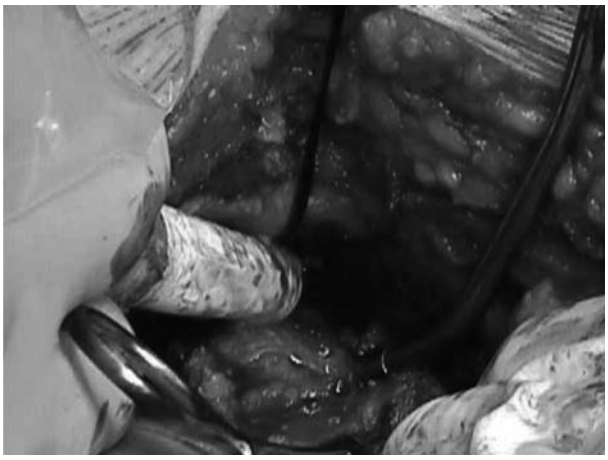
The ability of conventional imaging methods to detect pelvic lymph node metastases in patients with prostate cancer is rather restricted: pelvic computed tomography of clinically localized prostate cancer, has a low sensitivity for lymph node metastases; magnetic resonance imaging with lymphotropic super-paramagnetic nanoparticles seems promising. Nevertheless, this imaging technique is dependent on anatomical distortion and does not specifically explore the prostatic lymph node drainage. The concept of the sentinel lymph node (SLN) is based on the hypothesis that the lymphatic dissemination of neoplasms progresses in an orderly fashion: the SLN is defined as the first lymph node in a lymph node bed to receive lymphatic drainage from a tumour; it is the first lymph node that might be involved. The histological status of the SLN accurately predicts whether the rest of the lymph node chain is affected or not. This promising method has been adopted in patients with cutaneous melanoma or breast cancer, providing accurate staging and resulting in a low rate of morbidity through the avoidance of unnecessary lymphadenectomy.
Lymphoscintigraphy (LS) and radioguided sentinel node biopsy (RSNB) could be an alternative method of nodal staging in localized prostate carcinoma (4).

Materials and methods

Between June 2003 and February 2007 were included in our study 19 patients of mean age 66 (range 56-74) with prostate cancer, PSA 15,51 average ng/ml (range 3.69-62.70), Gleason score > 6 in the absence of bone metastases. Because it is performed transrectal ultrasound guided intraprostatic administration of 0.2 ml/190 MBq 99mTc bound to particles nanocolloid, prepared the day before surgery (Figure 1). Dynamic and static scans of the pelvis to 30', 60' and 120' were obtained immediately after injection.
Hot spots outside the site of administration were considered as sentinel nodes (SLNs). Prior to prostatectomy, is performed Limited Pelvic Lymphadenectomy. The presence of a marked node, identified by a gamma probe (Pol scintiprobe MR-100 Hi Tech.) slide slowly down the chain of lymphatic drainage, after LPL, puts the indication for an extended pelvic lymphadenectomy (Figure 2). All lymph nodes were then examined with hematoxylin-eosin staining and immunohistochemistry, with antibodies anticitocheratina.

Figure 1.
Transrectal ultrasound guided intraprostatic administration of 0.2 ml/190 MBq 99mTc.

Figure 2.
Intraoperatory detection of a marked node, identified by a gamma probe (Pol scintiprobe MR-100 Hi Tech.) slide slowly down the chain of lymphatic drainage.



Results

A sentinel node was identified in 17/19 patients with preoperative lymphoscintigraphy (identification rate 89%) and in 16/19 patients during surgery (84% discovery rate) with a negative predictive value of 97%. The most frequent site was identified at the level of hypogastric lymph nodes (23/41 LN→56%), outside the standard limited pelvic lymphadenectomy, followed by external iliac (13/41 LN→33%), obturator (3/41 LN→7%) and common iliac (2/41 LN→4%).
Lymph node metastases were detected by histological examination in 2 patients (13%); total metastatic nodes found were 9: 1 in the first, and 8 in second patient (first patient in a hypogastric lymph node and in the second patient, 7 external iliac lymph nodes and 1 in hypogastric).
Two metastatic nodes (22%) not removed by the limited pelvic lymphadenectomy were found with the sentinel lymph node dissection.

Discussion

The SLN is defined as the first lymph node in a regional lymphatic basin that receives lymph flow from a primary tumour. After intraprostatic injection of 99mTc-sulphur colloid (3), SLNs could be observed in the pelvic region in all patients. The radiotracer injected under transrectal ultrasound guidance was distributed into the peripheral

regions of each lobe of the prostate. According to prostate lymphoscintigraphy (5), these two regions drain in the same three directions: the main lymphatic pathway drains along the lateral bony wall of the pelvis (external iliac area and obturator fossa) to the angle of the internal/external iliac area, and then to the common iliac lymph nodes. Another pathway is represented by the perineal floor (pudendal internal iliac lymph nodes), which drains to the angle of the internal/external iliac area, too. Drainage to the sacral node basin is supposed to be a secondary site. Each lateral lobe of the prostate drains mainly into the ipsilateral group of lymph nodes with little crossover.
Possible causes of failure to identification are: failure to migration of the radiopharmaceutical from the site of administration; long period between LS and surgery, with inability of the probe during the dissection to highlight lymph nodes reported by the LS; accidental intravenous route, with early viewing lumbo-aortic lymph nodes in LS.
Current recommendations are to perform lymph node dissection of the obturator region and lymphatics around the external iliac artery when the preoperative serum PSA level exceeds 10 ng/ml, or the biopsy Gleason score exceeds 6, or the clinical stage is greater than T2. The hypogastric region is normally not included in the standard limited dissection.
However, various authors have compared limited lymph node dissection with extended dissection and concluded that lymph node dissection should include nodes along the internal iliac vessels for adequate staging (1).
Our findings using the SLN procedure confirm that the main area for SLNs is the hypogastric lymphatics, around the start of the internal iliac artery: 56% of patients had SLNs at this site.
That confirms the reliability of LS in the visualization of lymphatic drainage of the prostate and radioguided removal of sentinel lymph node (3).
In our experience there was only one case of false negative during the intraoperative detection of sentinel nodes by a gamma probe (Pol scintiprobe MR-100 Hi Tech.) slide slowly down the chain of lymphatic drainage after pelvic lymphadenectomy limited: the reason is sought probably in the long period between lymphoscintigraphy and surgery, with inability of the probe during the dissection to highlight lymph nodes reported by the LS.
Many of the hot nodes were found outside the standard dissection range (obturator fossa and external iliac regions), and metastatic nodes would have been missed by limited lymphadenectomy in two patients with metastases.
There are few publications on use of the SLN technique in patients with prostate cancer (1, 2). In our study, the SLN procedure permitted an optimal lymph node dissection range with minimal invasiveness, in the context of limited lymphadenectomy, and seems to be a useful method of staging prostate cancer also. Lymph node metastases were found outside the standard limited lymph node dissection area. LPL is insufficient to remove all the lymph nodes. A limited lymph node dissection would also remove nodes located along the initial centimetres of the hypogastric artery for representative staging.
Further studies should be performed to define the optimal indications. For example: Should sentinel lymphadenectomy alone be used in patients with low preoperative risk factors?
Which kind of lymphadenectomy (extended vs limited) should be employed in association with the SLN procedure in patients at high risk? Should the SLN technique be performed before radiotherapy?

Conclusions

The SLN procedure revealed the individual variability of the lymphatic drainage of the prostate. Standard limited lymph node dissection seems to be insufficient in patients with unfavourable prognostic factors (PSA >10 ng/ml, Gleason score > 6): lymphatic staging using the SLN procedure could be considered superior to limited lymph node dissection alone and could avoid the high morbidity of extended pelvic lymphadenectomy.
The SLN technique may lead to better treatment selection of patients with early prostate cancer but with unfavourable prognostic factors. Using ultrasound approach for preparing to lymphoscintigraphy and sentinel node research, is a valuable aid in the staging of localized prostate cancer.

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PRESENTATION

"And if a one night a renal colic..." The strange case of renal vein thrombosis without renal cancer.

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Summary

Introduction: *It is common experience to all urologists to manage many patients admitted at night from the casualty ward with a diagnosis of "therapy-resistant renal colic". However not all the patients with flank pain really suffer for renal colic, although painful somatic irradiation refers to the same areas.*

Case report: *A seventy years old male patient was admitted from the casualty ward for left renal colic. Laboratory tests showed normal creatinine, mild reduction of albuminemia, elevated triglycerides and cholesterol at the upper limit of normal. The pain had risen sharply a few hours before. For some years the patient suffered nocturia, but he never made an urologic consultation. Ultrasonography performed in the casualty ward demonstrated normal findings with no hydronephrosis but the presence of left perirenal extravasation with "casting-like" aspect and extending to the pelvis. Contrast-enhanced computed tomography (CT) revealed the presence of left renal vein thrombosis and acute segmental pulmonary embolism.*
The left kidney, apart from increased volume and reduced parenchymal impregnation, showed no neoplastic nodule. The case presented as unusual according to the opinion of consulted nephrologists, vascular surgeons and urologists (also from others hospitals and universities).
After informed consent of the patient (stressing seriousness and singularity of his condition), we decided to treat him as a deep vein thrombosis. We administered an heparin bolus (80UI/kg), followed by the infusion of heparin (18UI/kg/h) using a peristaltic pump for 14 days.
Results: *CT performed after 14 days of treatment showed the full resolution of renal vein thrombus and of pulmonary embolism. Thereafter a nephrotic syndrome was diagnosed and the patient was took in care by the nephrologist. Nephrotic syndrome preceded the hospital admission of the patient and was the etiological cause of renal vein thrombosis.*
Discussion: *The well known causes of acute flank pain reported in textbooks include renal and perirenal inflammatory processes, renal cell or transitional cell cancers of the kidney or of the urinary tract, obstruction of the urinary tract by stones or stenosis, hydronephrosis of different etiology whereas vascular causes are not often mentioned.*
Conclusions: *After the diagnosis of left renal vein thrombosis, the more probable associated urological is a renal cell carcinoma. Excluding renal cancer other possible causes of thrombosis are medical conditions such as amyloidosis, multiple myeloma, nephrotic syndrome, thrombophlebitis.*

KEY WORDS: *Renal vein thrombosis; Nephritic syndrome; Thrombolysis.*

INTRODUCTION

It is common experience to all urologists having to manage many patients admitted at night from Emergency Room with a diagnosis of "therapy resistant renal colic". But not all flank pain are really renal colic, although painful somatic irradiation refers to the same areas.

CASE REPORT

Seventy years old male patient admitted from the emergency room for left renal colic. Laboratory tests showed normal creatinine, mild reduction of albuminemia, elevated triglycerides and cholesterol at the upper limit of normal. The pain had risen sharply a few hours before.

Figure 1a.
(Renal superior pole). Left perirenal extravasation with "casting-like" manifestations until the pelvis.

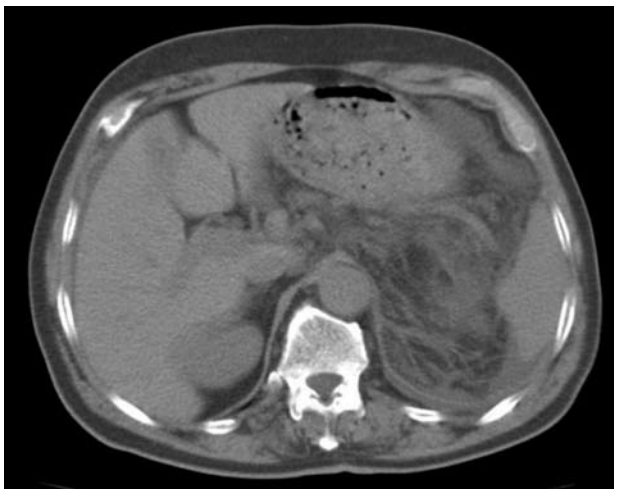


Figure 1b.
Bilateral hydronephrosis was absent. Left kidney, apart from the increased volume, showed no neoplastic nodule.

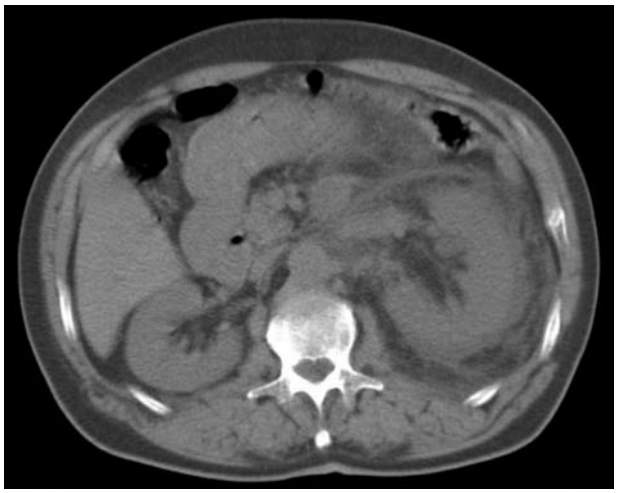
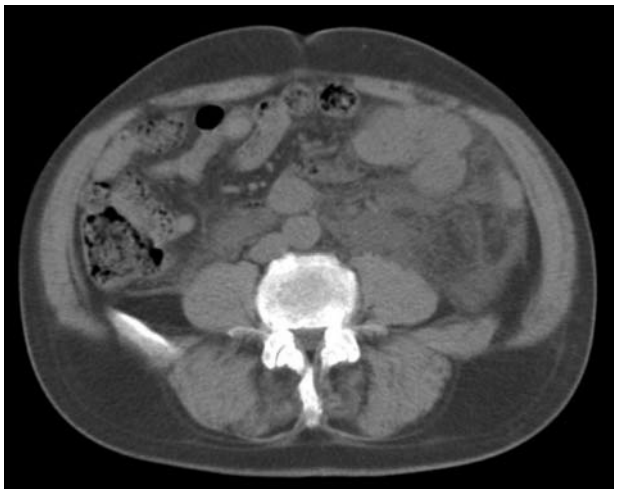


Figure 1c.
(Pelvis). Left perirenal extravasation with "casting-like" manifestations until the pelvis.



For some years the patient manifested nocturia, but never made an urologic consultation. Ultrasonography performed in Emergency Room detected all in standard condition, except of the presence of left perirenal extravasation with "casting-like" manifestations until the pelvis (Figures 1a-c; TC images. US images are not available). Bilateral hydronephrosis was absent. Therefore contrast-enhanced CT was performed and it revealed the presence of "the left renal vein thrombosis (Figure 2) and acute segmental pulmonary embolism" (Figure 3). Left kidney, apart from the increased volume and reduced parenchymal impregnation, showed no neoplastic nodule. We surveyed (by phone) nephrologists, vascular surgeons and urologists opinion, also in others hospitals and universities; none of them said to have dealt with a similar disease. Informed the patient and relatives about the gravity and singularity of case report, we decide to treat it as a deep vein thrombosis. We administered heparin bolus, followed by infusion of heparin 80UI/kg 18UI/kg/h using a peristaltic pump for 14 days (1).

Figure 2.
Contrast-enhanced CT reveals the presence of the left renal vein thrombosis.

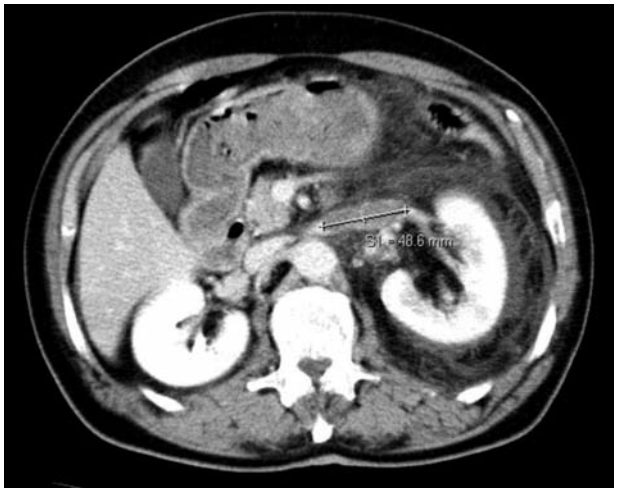
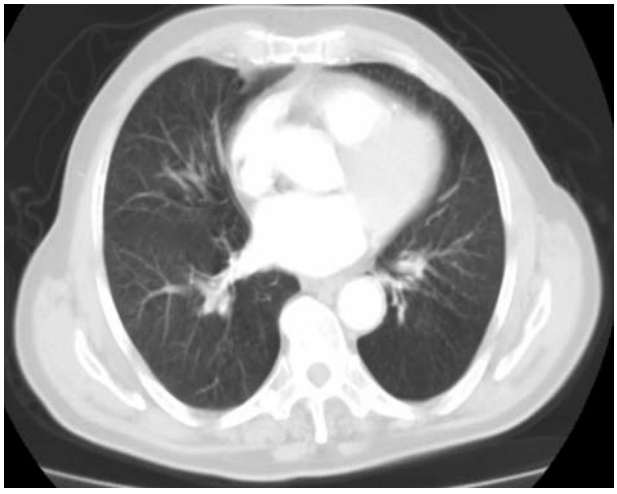


Figure 3.
Contrast-enhanced CT reveals acute segmental pulmonary embolism.



Results

CT performed after 14 days of treatment showed the full resolution of Renal vein thrombus and of pulmonary embolism. Meanwhile, the patient was took in care by nephrologists, because it was diagnosed a nephrotic syndrome. Nephrotic syndrome existed before hospital admission of the patient and was the etiological cause of renal vein thrombosis.

Discussion

Symptoms associated with numerous diseases can be indistinguishable from those of renal colic because receptors of many visceral organs as well as the body wall transmit sensation through pain fibers shared with the kidneys (2). Because of this overlap of the autonomic nervous system, patients have poor localization of visceral pain and findings at physical examination are often nonspecific.

This clinical overlap has made imaging indispensable for diagnosing renal colic in the emergency setting. Rucker CM et al. reported from a licterature rewiew that between 9% to 29% of patients presenting with flank pain may have an alternative diagnosis at unenhanced helical CT, most commonly adnexal masses, pyelonephritis, appendicitis, and diverticulitis (3). In fact, a renal or ureteral stone will be detected at CT in only 33%-55% of patients with acute flank pain. The causes of "real" renal colic from everyone known and reported by the texts of symptomatology include renal and perirenal inflammatory processes, renal cells or transitional cells cancers of the kidney or of the urinary tract, obstruction of the urinary tract by stones or stenosis, hydronephrosis of varied etiology. Vascular causes are hardly mentioned (4). Fortunately during the past 15 years, CT has become the standard of reference in the detection of urinary calculi due to its high sensitivity (95%-98%), high specificity (98%-99%). More important It is the ability to help delineate alternative causes of flank pain. When unenhanced CT demonstrates unilateral perinephric stranding or nephromegaly but no stones, the use of intravenous contrast material should strongly be considered. It may occasionally reveal more serious vascular conditions such as renal infarction, renal vein thrombosis, or renal artery aneurysm, which can also manifest with acute flank pain (3). Renal vein thrombosis usually develops as a secondary complication, most notably, the nephrotic syndrome. It may, however, occur as part of a primary disease process. Among the causes of renal vein thrombosis there are thrombosis of the inferior vena cava with secondary involvement of the renal veins, hypovolemia, primary renal disease, occlusion of renal veins by extrinsic or intrinsic involvement of the renal vascular pedicle (usually due to neoplasia and it has been reported in more than 50% of cases of renal cell carcinoma) (5), systemic disease usually associated with a hypercoagulable state (vasculitis, primary antiphospholipid syndrome, sickle cell disease, and the use of oral contraceptives), trauma, iatrogenic ones. Among primary renal diseases, renal vein thrombosis almost always occurs in patients who are nephrotic. The nephrotic syndrome by virtue of it being a hypercoagulable state is associated with an increased incidence of arterial and venous thromboembolism. Hypercoagulability is due to both an increase of prothrombotic factors (increased platelet activation, presence of high molecular weight fibrinogen moieties) and decreased antithrombotic factors (reduced antithrombin III). The incidence of renal vein thrombosis in the nephrotic syndrome ranges from 5% to 62% (6).

Conclusions

Once the diagnosis of left Renal vein thrombosis was made, it is clear that the only Urological cause of thrombosis is the neoplastic cause, when thrombosis is associated to a renal cells carcinoma. If we exclude the renal cancer, the remaining causes of thrombosis are of medical competence: amyloidosis, multiple myeloma, nephrotic syndrome, thrombophlebitis (7). But fortunately urologists are also good physicians.

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PRESENTATION

Distal ureter studied with endocavitary end-fire probe: Application in adult urology ultrasonographic clinic.

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Summary

Objective: *To evaluate the efficacy of transrectal or transvaginal Endocavitary Ultrasound (EU) to depict the juxtavesical and the uretero-vesical junction of the distal ureter.*

Methods: *We retrospectively examined a series of 80 patients with a variety of urological conditions affecting the distal ureter. EU was performed with a 6-10 MHz transrectal/vaginal end-fire probe. In all cases the length of visible ureter was measured. The series included benign and malignant affections as follows: 68 cases of distal ureteral stones and 12 malignancies (10 transitional cell carcinomas, 1 prostate cancer, 1 gastro intestinal stromal tumor). Gray scale and Color Doppler findings were anayzed and images were electronically stored. Every patient also undwent a transabdominal sonography. Definitive diagnosis was made with standard radiological imaging. In 4 patients we performed echo-guided endocavitary guided biopsies to obtain an histological diagnosis of ureteral solid lesions when transurethral biopsies were not feasible or negative.*

Results: *Length of visible ureter was 4 cm (SD 2.1). Ureteral stones were depicted in 80% of cases, however false negative were related to a stone localization above the last 4 cm of the visible distal ureter. The transabdominal approach depicted ureteral stones in 58% of cases. EU showed all the solid lesions located in the last 4 centimeters. Transabdominal approach showed a ureteral mass only in half of the cases. EU with Color Doppler (EUCD) was useful to evaluate the ureteral jet (presence or absence) and changes in the vasculature of solid lesions. Neither body habits, nor bladder fullness affected the reliability of the technique.*

Conclusions: *Our study shows that EU with end fire probe is a safe, minimally invasive and low cost technique for the investigation of pathological processes involving the lower part of the distal ureter.*

KEY WORDS: *Ureter; Ureter calculi; Ureter neoplasms; Ultrasonography; Interventional.*

INTRODUCTION

The distal ureter is defined as the portion of the ureter below the iliac vessels up to the meatus (1), including the uretero vesical junction (UVJ).

Distal ureter is involved both in malignant and benign diseases. Urolithiasis is the most common pathology affecting about 8% of the adult population (2). Sixty-five percent of all ureteral stones are located in the distal ureter (1).

Nowadays the use of computed tomography (CT) is the preferred diagnostic tool in relation to its high sensitivity and specificity for the study of the whole ureter (3-8). However CT requires instruments availability and implies patient exposure to ionizing radiation with high costs.

Endocavitary ultrasound (EU) seems to be promising for the study of the distal ureter given that transabdominal ultrasound (TUS) presents some limitations in the depiction of the distal ureter (9).

Ultrasound approach has several advantages: safety, easy available and low cost. The first report comparing EU (transrectal or vaginal) with TUS, was done by Holm in 1994 (10): he showed higher accuracy of the first technique over the former and iv urography in the study of the iuxtavesical ureter.

In the following years other reports were done using endocavitary US approach including echocolor Doppler (10, 13).

The aim is to evaluate the efficacy of endocavitary US in a retrospective series of patients affected by different pathological processes of the distal ureter.

Materials and methods

We retrospectively examined a series of 80 patients (mean age 54 years, 38 men and 30 women) affected by various urologic conditions of the distal ureter, evaluated with abdominal convex probe and transrectal/vaginal ultrasound equipped with end-fire convex probe. All procedures were performed in the ultrasound clinic at the Urology Institute in the general hospital for adults with the following indications: hydronephrosis including the distal ureter without stones at TUS or suspected disease or symptoms at the distal ureter. The benign group was composed by 68 cases with suspected distal ureteral stones. The malignant group was composed by 12 cases: 10 with urothelial cancer, 1 prostate cancer involving the bladder floor and the ureter (Figure 1) and 1 gastro instestinal stromal tumor.

We used a ultrasonography machine with 2-5 MHz convex abdominal probe and 6-12 MHz end fire endocavitary probe (Hitachi equipped with Astro 256 Esaote or Pro 5 Siemens). Examinations were performed by urologist or residents with experience in ultrasound. EU was performed with the patient in left lateral decubitus, before and after emptying the bladder and without fleet enema. After the probe was placed, the ultrasonic beam was initially directed to the postero-inferior aspect of the urinary bladder and then to the right or the left parasagittal plane, until the ureter was identified as a hypoechogenic tubular structure. We measured the length of the visible distal ureter in all cases. Gray scale findings were analyzed for the imaging of pathologic processes of the distal ureter. Endocavitary Ultrasound with Color Doppler (EUCD) investigation was then performed in order to evaluate the ureteral jet (presence or absence) and any vasculature changes in solid lesions of the ureter.

Four patients underwent EU guided biopsies in order to obtain a histological diagnosis of solid lesions. Indication to this approach was posed when transurethral biopsies were not feasible or negative.

Definitive diagnosis was supported by standard radiological imaging decided by urologist or by the medical staff at the hospital emergency department. EU and transabdominal ultrasound images were electronically stored.

Figure 1.
EU longitudinal view of a prostate cancer (k prostate) involving the ureter.

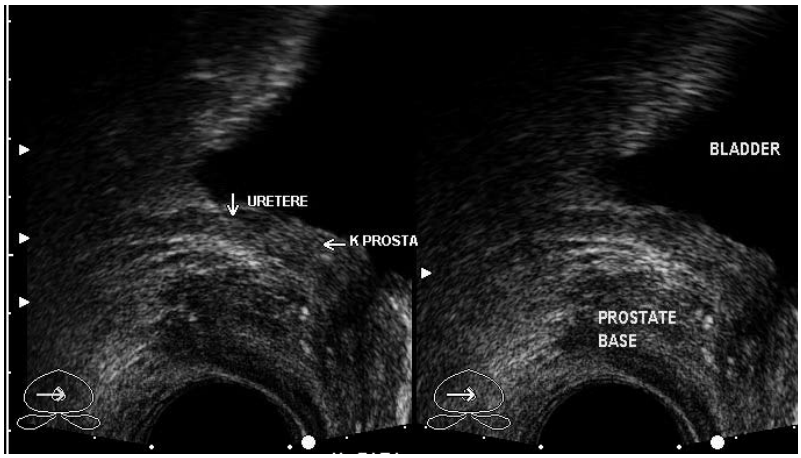


Figure 2.
EU longitudinal view of a small stone in the submucosal tract of the ureter. The twinkling sign (15) is visible at EUCD.

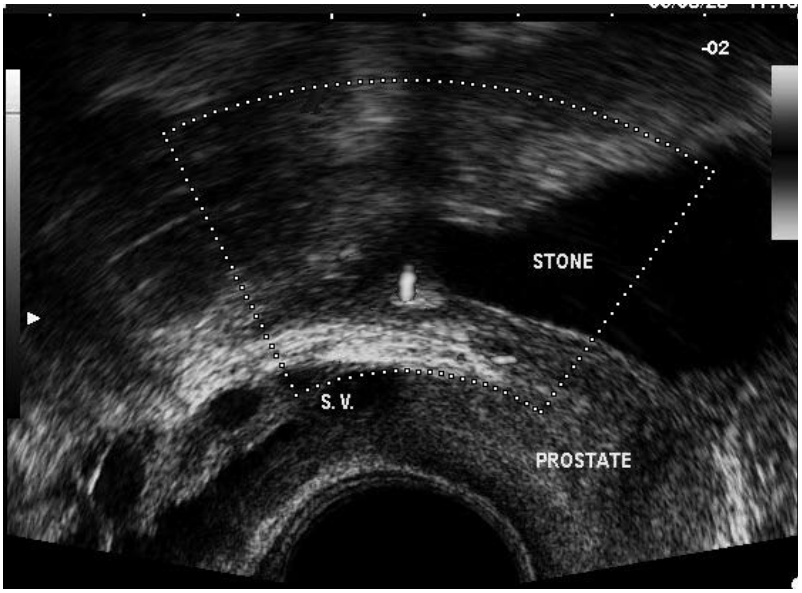
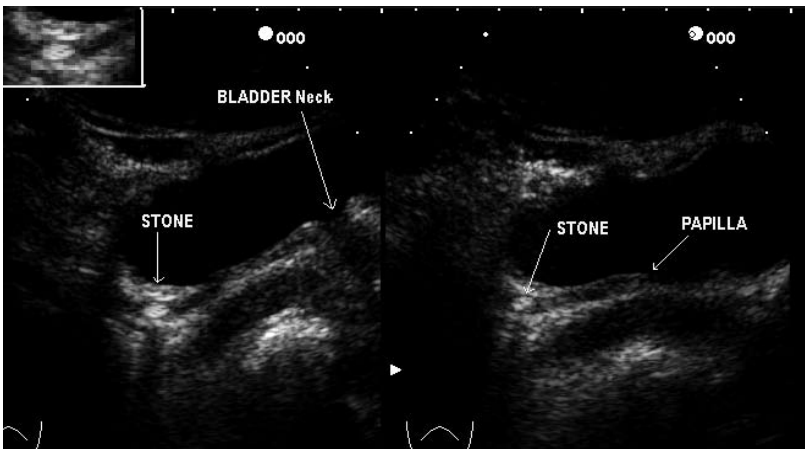


Figure 3.
Detection of a stone in the iuxtavesical ureter by TUS (longitudinal view).



Results

The mean length of the visible distal ureter at EU was 4.0 cm (SD 2.1). EU was able to show stone in the distal ureter in 80% of cases (54/68) (Figure 2). False negatives were related to stone location above the last 4 centimeters of the ureter. On the other hand the transabdominal approach allowed to identify stones in the distal ureter in 58% of cases (40/68) (Figure 3). EU accuracy was independent from body habitus and bladder fullness, while these factors were very important in abdominal approach. Considering the last 4 cm of the ureter, EU has the higher positive predictive value and negative predictive value over transabdominal US.

EU was able to identify all solid lesions located in the last 4 cm of the distal ureter (Figures 4 and 5). In few patients we saw hyperechoic images, similar to stones, related to calcifications of the tumor. EUCD findings were able to improve the diagnostic capacity, showing vasculature of the lesion. Transabdominal US showed a ureteral mass in less than a half of the patients (45%) and depicted ureter dilatation.

In 4 cases, target echo-guided biopsies were performed: viable tissue was obtained in all cases (Figure 6). Final histology was: urothelial carcinoma in 2, prostate cancer in 1 and 1 gastro intestinal stromal tumor. The interobserver variability was higher with transabdominal than with EU imaging.

Discussion

The transabdominal US has some disadvantages (9, 10): is operator dependent and image quality is affected by body habitus, obesity and surgical scars or radiotherapy. CT urography is a more sensitive and specific imaging technique for the study of the ureter (4-8), however in emergency setting unenanched CT is performed, that is expensive, not always available and exposes the patient to radiations

EU depicts with high accuracy the pathological findings of the last segment of the distal ureter, also called juxtavesical portion and the UVJ. EU has shown an high depiction rate for stones located in the juxtavesical portion of the ureterand in the UVJ (10, 11). Our report shows that EU has an higher capacity of depicting the distal ureter than transabdominal approach (90% vs 58%).

We were able to identify stones up to 3 mm. In such small stones the Color Doppler was useful to clarify the diagnosis. The gray scale assessment was able to establish the location of the stone (iuxtavesical, intramural or submucosal) and its size (12).

EU is not affected by body habitus, being a valuable technique also in obesity, pregnancy and also in patients with previous pelvic surgery or radiation. Bladder distension influences the acoustic window and the quality of the transabdominal ultrasound of the UVJ. On the other hand, EU is not affected by this factor (9). Thus, we believe that EU could be extended to patients who are unable to have bladder distension: severe symptoms, solitary kidney, acute renal failure or anuria. Some reports showed that gray scale plus EUCD study was superior to show the ureteral jet (12) and to differentiate benign from malignant processes of the ureter as the lat-

Figure 4.
EU oblique view of a urothelial cancer (lesion) involving the bladder floor and the uretero-vesical joint.

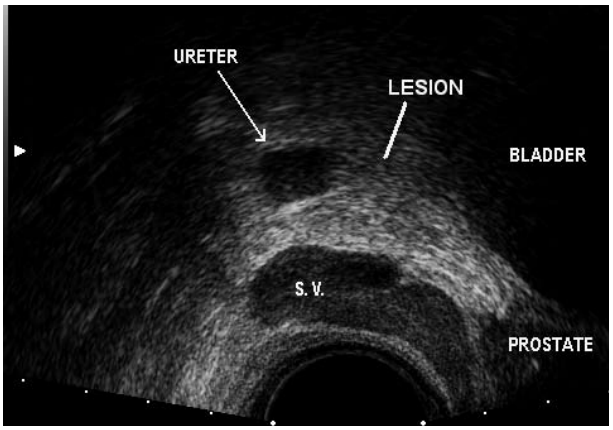


Figure 5.
EU longitudinal view showing hyperechoic solid lesion without acoustic shadow (obstruction).

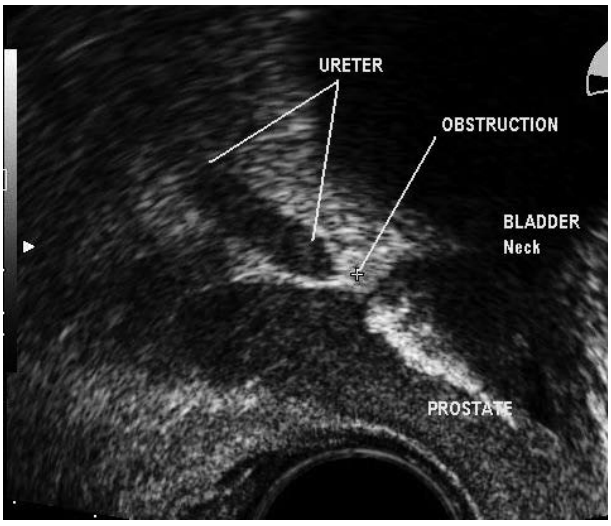
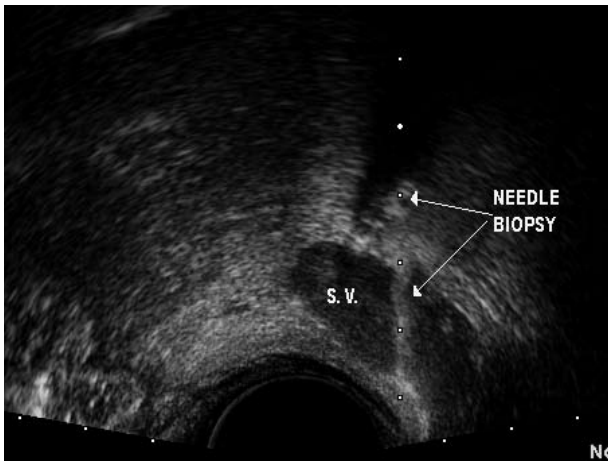


Figure 6.
EU transrectal needle biopsy of the lesion showed in Fig. 1.



ter showed a higher vascularization than benign affections (13, 14).
In our series EU proved to be useful to obtain transrectal biopsies under local anesthesia in selected cases. We also noticed a lower interobserver variability in EU than in transabdominal approach.
EU with end fire probe should be considered a minimally invasive tool in the diagnostic work-up of the distal ureter, the juxtavesical portion and the UVJ, with some elective indications:
– controindication to CT (severe obesity, reactions to contrast media, pregnancy)
– absence of a transabdominal acustic window (obese patients, ileum, previous pelvic surgery)
– reduced bladder capacity
– absence of urine output

EU disadvantages are the following:
– its accuracy is limited to the study of the last 4 cm of the ureter
– an operator with experience in this kind of diagnostic tool is needed
– enema is necessary in selected cases to obtain a good acoustic window
– "minimally invasive procedure", it needs patient's consent
– discomfort/pain in younger patients
– not feasible in patients without rectum or vagina (stenosis, surgery, …)

There are some limiting factors in our study: it is retrospective, not controlled and EU indications were not uniformly used by all medical staff. This study can be considered as case series, so that it has a low evidence accordingly to the levels of scientific evidence.

Conclusions

EU with end-fire probe can be a reliable diagnostic tool for the lower portion of the distal ureter (4 cm). This technique is cost effective, doesn't expose to radiation, is repeatable and is independent from abdominal acoustic window. EU does not need any preparation in most cases, is readily available in every urology unit. However it has a minimally invasiveness that could limit its use. EU with end fire probe should be considered a minimally invasive tool in the diagnostic work-up when clinical suspicion persist or hydronephrosis occurred and standard radiological imaging is negative or not possible.

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PRESENTATION

Contrast-enhanced ultrasound (CEUS) of lesions occupying renal space. Indications, limits, personal experience.

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Summary

In focal kidney disease, contrast-enhanced ultrasound (CEUS) using 2nd generation contrast enhancement allows continuous dynamic assessment of the arterial, venous and late perfusion phases of the renal parenchyma, as well as of focal lesions.
CEUS is particularly useful in cases of an uncertain diagnosis after the performance of unenhanced ultrasound (US) and echocolorDoppler (ECD) (e.g. dromedary humps, hypertrophic column of Bertin, outcomes of pyelonephritis), and for differential diagnosis of simple cysts with a suspicious appearance (e.g. cysts with a dense content, calcified cysts) and complex cysts of Bosniak types 2, 3 and 4. Instead, lesions shown to be solid at unenhanced US must be directly evaluated by computed tomography (CT) or magnetic resonance imaging (MRI), both to gain a panoramic view and because CEUS is often unable to reveal the precise nature of such lesions. In agreement with the literature, this experience (18 cases) confirms the utility of CEUS in the diagnosis of renal pseudolesions and complex cystic formations, reducing both the risk of radiation exposure and the use of the more costly CT and MRI methodologies.

KEY WORDS: *Contrast-enhanced ultrasound (CEUS); Renal pseudolesion; Kidney; Complex cysts.*

INTRODUCTION

During renal ultrasound assessments, clinically silent solid or fluid formations are often observed, as well as images due to anatomical variations or disease outcomes that can mimic a renal lesion. Unenhanced US, even supported by ECD, is often insufficiently diagnostic.
The introduction in clinical practice of 2nd generation contrast media (the most common medium in use nowadays is the Sonovue, Bracco, consisting of sodium hexafluoride-filled microbubbles) has raised new expectations and has indeed proven to be useful for various indications.
CEUS is particularly helpful in the differential diagnosis of doubtful findings at unenhanced US simulating lesions occupying renal space, (e.g. hypertrophied column of Bertin, fetal lobation, outcomes of pyelonephritis) and to evaluate complex cysts according to Bosniak's classification, whereas it appears to have a more limited value in the differential diagnosis of solid lesions.

MATERIALS AND METHODS

During the period 2006-2010, 19 patients were examined (11 females, 8 males, aged between 21 and 72 years) with doubtful US images of lesions occupying renal space, or with complex fluid or solid neoformations. The *Aplio Toshiba MS ultrasound device* was employed. Low MI CEUS was performed by injecting a 2nd generation contrast medium bolus (2.4 ml of *Sonovue, Bracco*) to study the vascular dynamics of the region of interest for 4-6 minutes (arterial, venous and late perfusion phases). Of these 19 patients, 3 had pseudotumours (1 had columnar hypertrophy, 1 an area of chronic pyelonephritis, 1 had fetal lobations and a cortical pseudolesion), 4 patients had unilocular cysts with a maximum diameter of 4 cm and a dense or calcified content, 4 patients had complex cysts with a maximum diameter of 3 cm, 7 patients showed solid hypo or hyperechogenic cortical masses with a maximum diameter of 5 cm, one of which was shown to be a local recurrence in a previously resected organ. In addition, CEUS, alternated with MRI, was used to monitor a case of a small renal tumour treated by RF thermoablation in an inoperable subject.

RESULTS

In the 3 patients with doubtful images at unenhanced US, CEUS excluded the presence of neoformations, showing an isovascular appearance of the regions of interest of the renal cortex and medulla in all the phases.

Table 1.
Classification of complex renal cysts according to Bosniak, adapted to CEUS by Robbin et al. (2003).

TYPE I	Simple cyst	No further investigation
TYPE II	Few thin septa or small peripheral calcifications	CEUS negative-stop CEUS with perfusion to the septa: CT: if negative, CEUS monitoring
TYPE III	Multiple thin or thick septa or small nodules: intermediate risk of malignancy	CEUS negative-CT, negative: CEUS monitoring CEUS and CT showing perfusion: surgical excision
TYPE IV	Many thick septa, nodules: high risk of malignancy	CEUS and CT negative: CEUS monitoring CEUS and CT positive: excision

All the unilocular cysts that were poorly visualized at unenhanced US (cysts with a corpuscular or dense content, one cyst in the left inferior pole with an extracortical extension) showed an avascular appearance in all the phases.
Among the patients with complex cysts, two showing thin, avascular septa in all the phases underwent six-monthly US monitoring, while another two with thick septa, in whom CEUS demonstrated perfusion, underwent CT scans, and subsequent surgical exploration confirming a malignant tumour.
In the 7 patients with solid neoformations showing a variable appearance at US: hypoechogenic, hyperechogenic or dyshomogeneous, a variable behaviour was also demonstrated at CEUS (3 with a vascular rim, hypo, iso or hypervascularized in the arterial phase, also depending on the presence of necrotic areas, that were generally poorly vascularized in the venous and late phases). All were shown by CT scan or MRI to be tumours, confirmed by the histological findings.

Discussion and conclusions

In agreement with data in the literature, in my personal experience CEUS is a useful tool: in cases where unenhanced US yields doubtful results (e.g. columnar hypertrophy, anatomical variants), CEUS assessment yielding negative findings is a simple, safe way to conclude the diagnostic work-up. This also applies in cases of unilocular cysts with a dense content (e.g. in intracystic hemorrhage, or artifacts like in some cases of cysts with an extrarenal extension).
Complex cysts (Bosniak types II, III and IV) are the best indication for CEUS: if the septa or solid intracystic areas show perfusion this may indicate malignancy and the diagnostic work-up should be continued with CT scanning. Instead, if there are few, thin septa without perfusion then monitoring with CEUS is sufficient.
As regards solid lesions my personal experience, although limited, confirms the absence of pathognomonic signs of malignant lesions. Therefore in these cases it is necessary to pass on directly to CT or MRI, also in order to gain a more panoramic view, except in few cases with contraindications to these imaging methods.
At present, routine performance of CEUS in kidney disease has not yet been regularly approved, so its use is considered off-label, justified by clinical needs in individual cases or if it is not possible to apply other methods. It is to be hoped that its use for some indications will be authorized, both to avoid radiation exposure and for economic reasons.

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Clinical use of ultrasonography associated with color Doppler in the diagnosis and follow-up of acute pyelonephritis.

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Summary

Objectives: *The purpose of this study is to evaluate the current role of the Ultrasound associated with the color-Doppler in the diagnosis of acute pyelonephritis (APN) and to compare ultrasound images with CT images in order to reduce the amount radiation absorbe without significant loss of diagnostic efficacy, since this disease in most cases affects young adults.*

Material and Methods: *We studied 38 patients (aged 17-65 years) who presented from September 2007 to March 2010 to the emergency department with suspected diagnosis of APN. All patients underwent first to an ultrasound study, then to abdominal CT. Renal, perirenal and extrarenal tomographic findings usually associated with acute pyelonephritis were analyzed, in an attempt to identify what are the differences withrespect to the images obtained with an ultrasound study. All patients then performed ultrasonography and/or abdominal CT evaluation one month later, 25 patients repeated both examinations, while the other 13 repeated only ultrasound.*

Results: *In 38 subjects with suspected APN, CT assessed the presence in 79% and in 21% the absence of the disease. Ultrasonography in 68% of cases diagnosed APN, by an increase in kidney size related to the presence of hypoechoic areas associated to edema, blurred margins and reduction of the color-Doppler vascularity. Ultrasound associated with the use of color-Doppler revealed a sensibility of 76% and specificity of 75%. Color and power-Doppler have better diagnostic accuracy than basic gray scale ultrasound, in the diagnosis of focal pyelonephritis.*

Conclusions: *Therefore the combined use of ultrasound and color-Doppler can obtain useful information about the diagnosis and follow-up of the disease, with an improvement in terms of cost, without significantly altering the diagnostic efficacy and reducing the amount of radiation absorbed.*

KEY WORDS: *Acute pyelonephritis; Ultrasonography; Computed tomography; sensibility.*

INTRODUCTION

Urinary tract infections (UTI) are considered the most common bacterial infection, but their actual impact remains unknown because epidemiological this type of infection is still not subject to complaint in many countries. United States data source, however, speak 7 million outpatient visits a year for urinary tract infections, to which we must add at least another million emergency department visits and approximately 100.000 hospitalizations (1). For most urinary pathogens are Gram-negative, usually present in the intestinal flora. The Escherichia coli is the causative agent in 85% of female infections. Other Gram-negative enterobacteria that occur less frequently and cause between 5% and 10% of UTI are *Proteus* and *Klebsiella*.

Although Gram-positive organisms as *Staphylococcus saprophyticus* and *Enterococcus faecalis* can cause urinary tract infections (10-20%) (2, 3). The bacteria reach the kidney or by hematogenous or ascending from lower urinary tract causing acute renal inflammation.

Acute pyelonephritis (APN) is an inflammatory disease based infectious kidney (renal pelvis and parenchyma) that most often affects young-adult female flowing if not

well diagnosed acute renal failure, bacteremia and sepsis (4). The diagnosis of acute pyelonephritis is based on the combined use of history, exam objective, clinical, laboratory and diagnostic imaging. The clinical signs are given by an abrupt onset of fever with chills, temperature > 38,0°C, unilateral or bilateral flank pain, and sometimes gastrointestinal symptoms such as nausea, vomiting and diarrhoea that may confuse the diagnosis. Laboratory tests show pyuria, leukocyturia, hematuria, cultural examination of urine and blood positive. Blood tests may show leukocytosis with a shift of neutrophils, increased erythrocyte sedimentation rate, elevated C-reactive protein. Diagnostic imaging, in particular, plays a major role in selecting the clinical scenarios, helping to put a differential diagnosis with other pathological conditions, check functional or structural abnormalities that may require intervention, characterize the severity of the infection and make follow-up over time, assessing the extent of organ damage following an acute infection resolved.
Ultrasound associated with color-Doppler is commonly used as a method of first instance, for its spread, speed of use, low cost and absence of radiation doses. The purpose of this study is to take stock of the current role of the Ultrasound associated with the color-Doppler in the diagnosis of APN and to compare ultrasound images with CT images in order, without altering significantly the diagnostic efficacy, reduce the amount radiation absorbed, since this disease in most cases affects young adults.

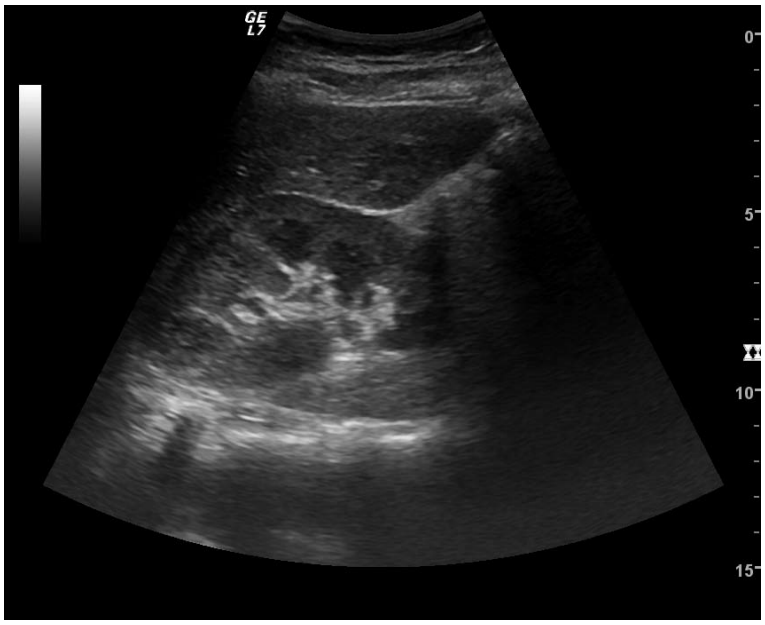
Material and methods

This study evaluated patients arrived at the *Urology's Unit Arcispedale "S. Anna" of Ferrara* between September 2007 to March 2010 by emergency department with suspected diagnosis of APN and were included in the present retrospective, transversal and observational study.
The criteria for inclusion were clinical symptoms such as unilateral or bilateral acute pain within the flank (radiating to the loin, abdomen, and/or groin), a fever of 38,0°C or more, a leukocytosis count exceeding 10,000/µl, the presence of white blood cells of more than 5/high-power fields on the urinary analysis. We studied a total of 38 patients (20 women and 9 men) aged between 17 and 65 years. All patients underwent first to a ultrasound study, also by the same operator, with the use of ultrasound *Logiq 7 General Electric* with a multifrequency convex probe and then to abdominal CT (helical CT apparatus of *General Electric*) the contrast-enhanced images were acquired after intravenous injection of iodinated non ionic contrast agent. All of the studies included a non-contrast enhanced phases, with nephrographic and pyelographic images from the diaphragm up to the pubic symphysis.
All patients then performer ultrasonography and/or abdominal CT inspection one month later, 25 patients were repeated in both, while the other 13 have only repeated ultrasound control at a distance of 1 month after discharge.
Acute pyelonephritis was classified into: a) unilateral or bilateral; b) focal or diffuse; c) with or without nephromegaly; d) complicated or no-complicate (with or without renal/perirenal abscess).
Renal, perirenal and extrarenal tomographic findings usually associated with acute pyelonephritis were analyzed, in an attempt to identify what are the differences with the images obtained with an ultrasound study.
The following renal and perirenal findings were taken into consideration:

a) nephromegaly: longitudinal renal axis > 11 cm and/or focal or diffuse asymmetry of renal dimensions;
b) heterogeneous nephrogram: areas of hypoperfusion on the renal parenchyma;
c) perirenal fat heterogeneity: characterized by striated nephrogram, increased density of the perirenal fat and thickening of Gerota's fascia;
d) collecting system dilatation;
e) nephrolithiasis and ureterolithiasis: presence of calculus in the collecting system;
f) renal and perirenal abscess.

In the ultrasound diagnostic criteria may be noted an increase in size of the kidney due to swelling of the parenchyma. The structural changes are more difficult to detect: diffuse micronodular forms can be seen both an increase in echogenicity, or more frequently a reduction in echogenicity associated edema and inflammation. In diffuse forms macronodular appears parenchymal inhomogeneity or isoechoic regions, indistinguishable from the renal parenchyma, hypoechoic and rarely hyperechoic (5, 6) (Figure 1). The color and power-Doppler include a decrease in the area of inflammation that could promote recognition ultrasound.

Figure 1.
Ultrasound image of acute pyelonephritis macronodular. Longitudinal scan of kidney shows reductions in parenchymal echogenicity associated with edema and infiammation.

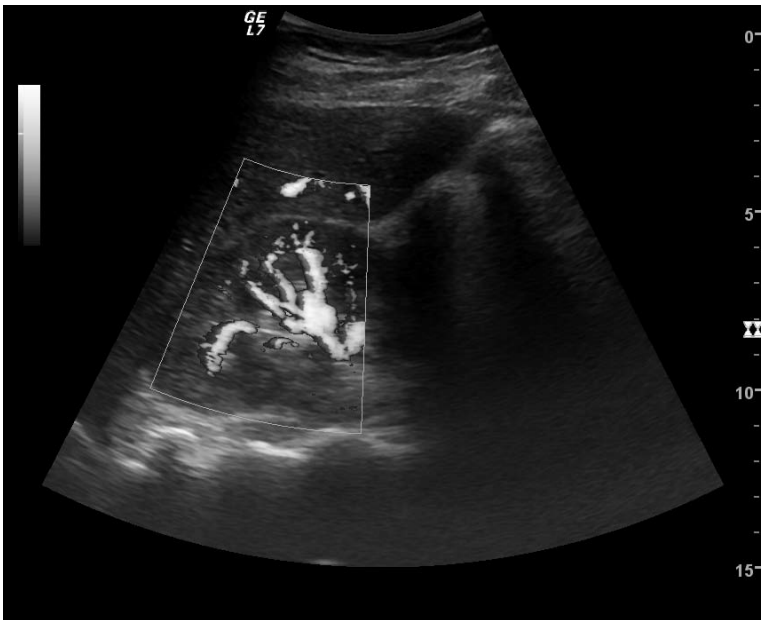


Forms of focal renal inflammation translate ultrasound with an area circumscribed hypoechoic or anechoic with reinforced rear wall to discretely defined contours.
These lesions are differentiated from renal cysts and renal abscess (which has to be larger than the focal nephritis, sharp focus, not frank echostructure for the presence of low-level echoes that translate the presence of necrotic material in context).
Collections inflammatory perirenal translate as a hypoechoic or anechoic areas that wrap the kidney. These areas can sometimes look more echogenic due to inflammatory phenomena of organization, which can be confused with the structure reflecting impairment of the lodge. Collections extrarenal function should be assessed in their extension in the back peritoneum, but often the intestinal gas and skeletal structures that proper evaluation of the extension downwards (7-9, 11).

Results

The results analysis demonstrated findings of unilateral acute pyelonephritis in 36 cases (20 at right and 16 at left), and bilateral en only two case, in a total of 38 kidneys affected by disease.
Acute pyelonephritis was classified as focal and multifocal, respectively, in 10/38 (26%) and 28/38 (74%) of cases; with and without nephromegaly, respectively, in 16/38 (42%) and 22/38 (58%) of cases; and complicated and non-complicated, in 7/38 (18%) and 31/38 (82%) of cases.
In 38 subjects with suspected APN, CT was to assess the presence in 79% (30/38) and absence of disease 21% (8/38). Ultrasonography in 68% (26/38) of cases found in the diagnosis of APN, as reflected in an increase in kidney size related to the presence of hypoechoic areas associated edema with blurred margins and a reduction of the color-Doppler vascularity while in 3 cases was positive for the outbreak of APN is not confirmed at CT.
We found only two cases of hyperechogeicity, which were propably related to pus in renal tubules. Moreover, we identified those cases of hyperechogenicity on a second examination after vascular defects were revealed by color and power-Doppler sonography.
For cooperative patients, power-Doppler sonography allows vascular mapping of the kidneys. The normally straight course of interlobar arteries around the pyramidis is visible on both axial and longitudinal scans. Where APN is present, an area of hypovascularity is identified. This area is often triangular. Peripheral interlobar arteries compressed by adjacent edematous parenchyma appear curvilinear rather than straight and could be compared with the claw of a bird of prey (10) (Figure 2).
The 8 cases of APN unrecognized ultrasound examination were focal parenchymal forms, tested positive for abdominal CT, two of these 8 patients are among the first patients included in the study and one is an obese man of 57 years.
In three patients with clinical and biologic findings of APN, thickening of the renal pelvis, a frequent and non specific finding, was shown by B-mode sonography, whereas color-Doppler sonography and CT findings were normal.
Acute pyelitis with no nephritis was a possible diagnosis in these patients.
An entity such as theirs was described as on upper urinary tract infection confined to the ureter and the pelvicaliceal system. Although isolated pyelitis should probably not damage the renal parenchyma, these patients were treated as usual for APN.
Ultrasound associated with the use of color-Doppler revealed a sensibility of 76% and specificity of 75%.

Figure 2.
Power Doppler sonogram of acute pyelonephritis. Longitudinal scan of right kidney shows areas of decreased flow.



Discussion

Ultrasound is somewhat less sensitive than CT, especially in focal parenchymal forms, where you have to do differential diagnosis (simple renal cysts, renal abscess), so it must be done with the help of color-Doppler, demonstrating low-level echoes in context of inflammatory areas, coupled with a reduction in those areas of vascularization in order to promote recognition ultrasound.
Ultrasound also has proven highly effective in the follow-up of these injuries during medical therapy, exposing the subject to a lower dose of radiation, including in relation to the need for frequent monitoring of patients throughout the treatment period.
Color and power-Doppler have better diagnostic accuracy than ultrasound basic gray scale, in the diagnosis of focal pyelonephritis.
The ultrasound contrast agent can detect the presence of an acute focal pyelonephritis when the renal vessels are compromised surrounding edema. In this case the area affected by the infectious process presents a trian-

gular shape, similarly to defects of renal perfusion (12, 13). The focal areas affected by kidney infection process is often less visible after administration of contrast ultrasound than they appear on base in gray scale and color-Doppler. This is explained by the fact that the microbubbles are entirely intravascular and renal vessels are visible in focal areas are infected, while the color-Doppler shows only the large renal vessels that are displaced by the presence of inflammatory edema (14).

If it is obvious that the purpose of diagnostic imaging tests is to perform the highest quality possible to achieve as accurate diagnosis, not always taken for granted today. The doctor is no longer required to use only methods that are effective and decisive in the clinical management of the patient, but also to choose the best methods and procedures using as yardstick, even the cost-effectiveness analysis.

Conclusions

Therefore the combined use of ultrasound and color-Doppler can obtain useful information about the diagnosis and follow-up of the disease, with an improvement in terms of cost, without significantly altering the diagnostic efficacy, reducing the amount of radiation absorbed, given that disease in most cases affects young adults.

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PRESENTATION

Surgical complications of renal transplantation: Ultrasound diagnosis.

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Summary

Objective: *Ultrasound is the principal imaging technique for the evaluation of a renal allograft; it is a safe imaging technique to assess the structure of the graft and its perfusion without the need for intravenous contrast or ionizing radiation. The evaluation of kidney transplant complications is easy due to its presence in the iliac fossa lying anterior to the external iliac vessels. Complications may be classified as medical and surgical; the latter are classified in urologic, vascular and general surgical complications.*

Materials and Methods: *Our experience on surgical complications in kidney recipients from donors, on the role of ultrasound in the diagnosis of these complications and their impact on the graft and patient survival rates is reported.*

Results: *Ultrasonoghaphy represents a safe imaging technique to assess the structure of the graft and its perfusion without the use of ionizing radiation and iodinated contrast medium, and a quick, accurate method for the evaluation of complications.*

Conclusions: *Although it possesses limitations and is ultimately operator dependent, ultrasound is considered an excellent tool for the assessment of the kidney transplant and in our experience it represents the main imaging technique used in the evaluation of graft complications.*

KEY WORDS: *Kidney transplantation; Ultrasound; Lymphocele; Hydronephrosis; Vascular complications.*

INTRODUCTION

Ultrasound is the principal imaging technique for the evaluation of a renal allograft; it is a safe imaging technique to assess the structure of the graft and its perfusion without the need for intravenous contrast or ionizing radiation. The assessment of the kidney transplant is easy due to its presence in the iliac fossa lying anterior to the external iliac vessels. Evaluation of the graft includes assessment of the size and volume, parenchymal echogenicity, cortico-medullary differentiation, collecting system, and surrounding soft tissues. Color Doppler Imaging allows rapid assessment of global renal arterial perfusion and venous patency. It also allows visualization of the main, anterior and posterior divisional, interlobar, and arcuate arteries and corresponding veins within the graft. The normal transplant kidney has a low resistance arterial vascular bed and the main renal artery shows normal Doppler waveform with flow velocity ranging between 20 and 52 cm/sec. The *Resistive Index* (RI) is a widely used measure of resistance to arterial flow within the renal vascular bed and is calculated from the pulsed Doppler arterial waveform. An RI of less than 0.7-0.8 is considered normal (1), whereas an RI in excess of 0.9 is a strong indicator of graft dysfunction.

Complications may be classified as medical and surgical; the latter are classified in urologic, vascular and general surgical complications.

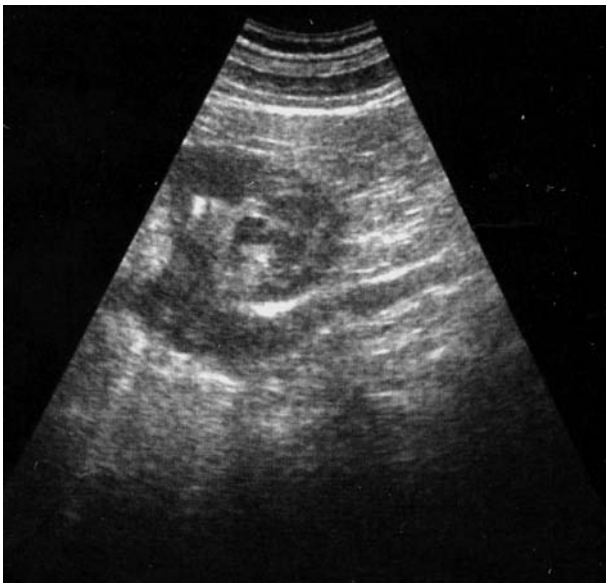
UROLOGIC COMPLICATIONS

Urologic complications occur in 5-10% of renal transplants and are associated with mortality rates of up to 22%. Death or transplant loss is more common when these complications occur within 3 weeks of surgery (2, 3).

Collecting system dilation

Collecting system dilation may be obstructive or nonobstructive. Obstruction of the transplant collecting system may occur secondary to extrinsic processes (e.g., peritransplant fluid collection), ureteral stricture (as a consequence of vascular insufficiency or rejection), or intralu-

Figure 1.
Collecting system dilation.



minal lesions, such as kidney stone, blood clot, or sloughed papilla (4). A mild, self-limited obstruction may result from early postoperative edema at the ureteroneocystostomy site, and minimal dilation may persist despite resolution of obstruction. Other causes of nonobstructive collecting system dilation include a full bladder, rejection, infection, and resolved, prior obstruction. This latter cause of nonobstructive dilation is particularly relevant in the transplanted kidney, because the collecting system is denervated and has no tone.

The most reliable noninvasive method to diagnose obstruction is progressive collecting system dilation on serial sonograms (Figure 1). Antegrade pyelography or a Whitaker pressure-flow study may be necessary to determine whether collecting system dilation has an obstructive or nonobstructive cause. Nuclear medicine imaging of ureteral obstruction, typically shows normal perfusion and parenchymal uptake of tracer by the transplant, but pooling of tracer in the renal pelvis and prolonged pelvic retention. An obstructed system does not respond to the administration of diuretics such as intravenous furosemide. A system with an emptying half-time of more than 20 minutes is considered obstructed (normal emptying half-time is less than 15 minutes).

Urinary fistula and urinoma

Urine leaks and fistulae occur in 2-5% of grafts and account for half of the urologic complications (5, 6). Urinomas resulting from extravasation of urine from the renal pelvis, ureter, or ureteroneocystostomy usually occur in the first 1 to 3 weeks after transplantation and may be caused by disruption of the ureterovesical anastomosis, incomplete bladder closure, ischemia of the collecting system, postbiopsy injury, or severe obstruction. Urine leaks may be undetectable by ultrasound when small, but present as localized fluid collections or urinary ascites as they enlarge. Urinomas typically manifest as cystic fluid collections in the pelvis adjacent to the ureter and separate from the bladder. They may enlarge rapidly, but generally do not have septations unless infected. Diagnosis can be established by ultrasound-guided needle aspiration which shows a high creatinine level in the fluid. Needle aspiration readily distinguishes a urinoma from postoperative hematoma or lymphocele, the latter having a creatinine level comparable to serum.

General surgical complications

Hematoma

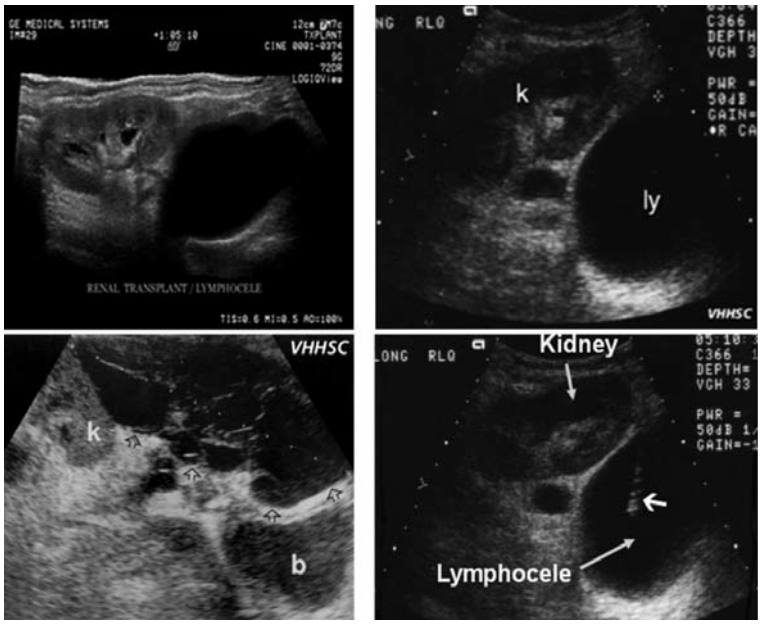
Hematomas are common in the immediate postoperative period, they may be extrarenal or subcapsular in location, and usually resolve spontaneously. They may also occur after a biopsy or result from rupture of a graft pseudoaneurysm. On occasion, the hematoma may be large enough to obstruct the ureter. The ultrasound appearance of a hematoma varies with time, being echogenic in the acute phase and decreasing in echogenicity as clot lysis occurs.

Lymphocele

Lymphoceles are the most common type of peritransplant fluid collection and are the product of extraperitoneal or renal lymphatic disruption at surgery or during graft harvesting. They usually occur several weeks to months after surgery (7, 8). The incidence of lymphoceles has been reported to be higher when rapamycin is used for early posttransplant immunosuppression. Small lymphoceles are common and are usually asymptomatic, but larger ones can cause obstruction.

The typical ultrasound appearance of a lymphocele is a

Figure 2.
Lymphocele.



fluid collection inferior and medial to the transplant that often contains septations and low-level echoes (Figure 2). Diagnosis can be confirmed by needle aspiration which shows a creatinine level equivalent to serum.

Abscess

A peritransplant abscess is usually secondary to infection of a preexisting fluid collection and generally occurs 4 to 5 weeks after transplantation. The ultrasound appearance is a fluid collection that contains debris, low-level echoes, and occasionally gas; the latter manifests as mobile, nondependent, echogenic foci with "dirty" shadowing or "ring-down" artifact.

VASCULAR COMPLICATIONS

Renal artery thrombosis (RAT)

Renal arterial thrombosis is an uncommon complication of transplantation and usually occurs in the early postoperative period.

RAT is most commonly a consequence of technical problems at the arterial anastomosis. Other causes are: thrombogenic state, severe acute rejection, and progression of a stenosis to thrombosis. The findings in color and pulsed Doppler imaging consist of absent arterial and venous blood flow within the graft (9). There is some controversy regarding the necessity of further imaging to confirm this diagnosis because there are several reported cases in which no flow was demonstrated by Doppler, but digital subtraction angiography revealed patent vessels.

Renal artery stenosis (RAS)

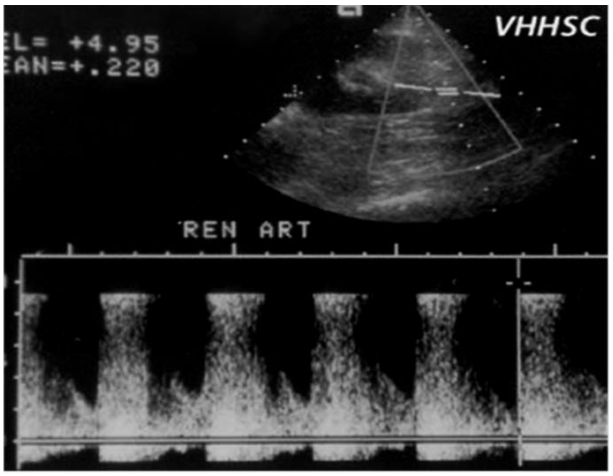
RAS develops in up to 12% of transplants and almost always occurs within 1 cm of the anastomosis (10). It is usually a consequence of neointimal hyperplasia near the anastomosis, but post-anastomotic strictures may occur following rejection. Clinical findings suggestive of RAS include insidious rise in creatinine accompanied by hypertension and a bruit over the graft. Ultrasound will show a structurally normal kidney in RAS. The diagnosis of RAS by Doppler ultrasound is made by demonstration of a focal, segmental region of flow abnormality, characterized by elevated PSV and turbulent flow. Aliasing and perivascular colour assignment may be seen in high-grade stenoses (Figure 3). Various threshold values for PSV have been proposed for optimal detection of RAS, ranging from 100 to 300 cm per second; reported sensitivities and specificities range from fair to excellent. Because the normal range of PSV in the transplant renal artery may be variable, a ratio of PSV in the renal artery compared with the external iliac artery may be more useful.

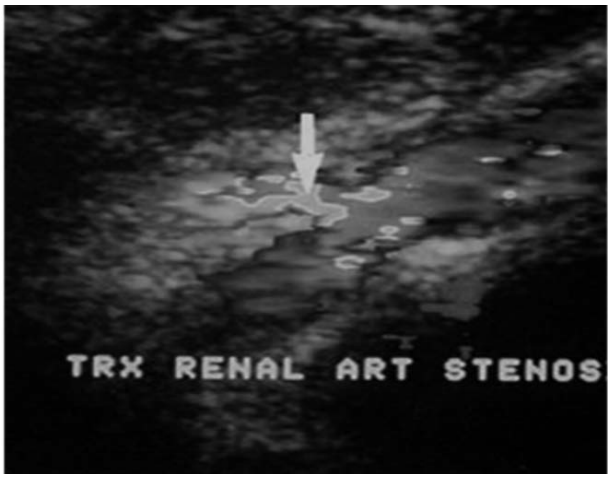
The accurate calculation of velocity by the machine's software, however, is highly dependent on the accuracy of the operator's estimate of the angle of insonation, and errors in this regard can yield spuriously elevated velocities.

The accuracy of this estimate (angle correction) is dependent on the adequacy of delineation of the course of the renal artery, which is often small and tortuous. Color and power Doppler, by providing a map of the vascular anatomy, are helpful in tracing a vessel and therefore in determining the appropriate angle. A confident diagnosis of RAS using Doppler ultrasound can be made if the characteristic findings occur in a well-delineated vessel, allowing accurate angle correction. Conversely, high velocities without associated turbulence in a region where the accuracy of angle correction is equivocal must be viewed with skepticism.

A pathologically low RI within the graft (0.6 or less) may be highly specific for stenoses over 50%. Reduction in pulse amplitude and delayed systolic upstroke on PD (parvus-tardus phenomenon) may be identified within the renal parenchyma downstream from a significant stenosis (11, 12). This waveform, characterized by an acceleration index less than 3 m/s² or a systolic acceleration time over 0.07 s should be considered strong evidence of a high-grade RAS. Regardless of the sonographic findings, angiography must be performed when clinical suspicion of RAS is high.

Figure 3.
Renal artery stenosis.





Renal vein thrombosis (RVT)

Renal vein thrombosis is an uncommon complication that usually occurs in the first postoperative week and constitutes a surgical emergency. It usually occurs as a result of extrinsic compression of the graft or kinking due to excessive length of the vein or mobility of the graft. Rarely, technical complications at the graft anastomosis site may lead to thrombosis. These patients present with oliguria or anuria and elevated creatinine in the immediate postoperative period. The sonographic features of renal vein thrombosis include an enlarged kidney with absent venous flow on color doppler or power doppler imaging. A distended thrombus-filled main renal vein is diagnostic of this entity but absence of the finding does not exclude the disorder. A prolonged "U-shaped" or plateau-like reversal of arterial flow in diastole is characteristic of RVT, and when seen in combination with absent renal venous flow on CDI should suggest the right diagnosis (13, 14).

Arteriovenous Fistula (AVF)

An AVF occurs as a consequence of simultaneous laceration of a renal artery branch and an adjacent vein during biopsy. These occur in up to 18% of biopsied kidneys but are almost always small and asymptomatic. Postbiopsy arteriovenous fistulas most often resolve spontaneously but can produce persistent hematuria or hypertension. Color Doppler imaging features of AVF include: focal colour aliasing within the nidus and perivascular colour assignment at low flow velocity settings due to tissue vibration artifact (15). The hallmarks of AVF on Power Doppler include low resistance, high velocity arterial flow within the feeding artery and high velocity arterialized venous flow in the associated draining vein.

Table 1.
Baseline Donor and Recipient Characteristics.

	Group A (n = 202)	Group B (n = 396)
Donors		
Mean Age	67	35
Hypertension	70.1%	12.5%
Diabetes	1.1%	0.5%
Creatinine clearance	59.7 ± 28,7	96 ± 26
Death from cerebrovascular accident	76.1%	30.8%
Recipients		
Mean age	52	41.5
Weight (Kg)	66	64
Dialysis (months)	78.8 ± 59.5	79.3 ± 57

Table 2.
Comparison of Outcome Data.

	Group A (n = 202)	Group B (n = 396)	p-value
Delayed graft function	92 (45.5%)	71 (17.9%)	P < 0.001
Primary non function	8 (3.9%)	5 (1.2%)	P = 0.06
Acute rejection	13 (6.4%)	22 (5.5%)	P = 0.8

Table 3.
Surgical complications.

	Group A (n = 202)	Group B (n = 396)
Urological	7.2%	1.5%
Vascular	6.4%	3.3%
General surgery	17%	8.0%

Our experience

The demand for kidney transplantation has increased dramatically in the last years and the critical shortage of organs available for transplantation has led to alternative strategies to expand donor pool. The use of kidneys from expanded criteria donors (ECD) represents an option to reduce the disparity between organ supply and demand (16-20). Our experience on surgical complications in kidney recipients from such donors, on the role of ultrasound in the diagnosis of these complications and their impact on the graft and patient survival rates is reported. From 1998 to 2009, 638 kidney transplantations were performed: 202 (37.9%) from ECD (group A) and 396 (62.1%) from optimal donors (group B). Donor and recipient characteristics are summarized in Table 1. After a mean follow-up of 60.3 months, delayed graft function (DGF) requiring dialysis was observed in 92 (45.5%) group A and in 71 (17.9%) group B recipients, respectively (P < 0.001). No significant differences were observed in primary non function (PNF) and acute rejection episodes among the two groups (Table 2). Surgical complications were observed in 62 (30.6%) of group A and in 51 (12.8%) of group B recipients (P < 0.001) (Table 3). In all the cases, ultrasonography was the principal imaging technique for the evaluation of the graft complications. When peritransplant fluid collections were observed, characterization of the fluid was achieved by obtaining a sample using ultrasound-guided aspiration and then determining the creatinine concentration.

Conclusions

The clinician evaluating a patient with renal transplant dysfunction has the choice of a variety of imaging procedures, including ultrasound, nuclear medicine, computed tomography, magnetic resonance imaging, and excretory urography. Imaging evaluation is usually initiated with ultrasound, which represents a safe imaging technique to assess the structure of the graft and its perfusion without the use of ionizing radiation and iodinated contrast medium. It is also relatively easy to perform in the pediatric population, unlike other cross-sectional techniques, because it does not require the child to be immobilized. Gray-scale ultrasound in the current era offers excellent detail and resolution, and the advent of Doppler examinations allows assessment of vascular

flow. Although it possesses limitations and is ultimately operator dependent, ultrasound is considered an excellent tool for the assessment of the kidney transplant and in our experience it represents the main imaging technique used in the evaluation of graft complications.

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PRESENTATION

Ultrasound imaging diagnostics: Healthcare risks for urologists.

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Summary

Objectives: *The objectives of this study are: 1) assessing if Ultrasound (US) used during US scans can represent a risk for the healthcare of urologists; 2) verifying the frequency of Carpal Tunnel Syndrome (CTS) symptoms and musculoskeletal disorders (MSD), trying to assess the possible correlation with job load and US scanning procedures; 3) assessing the role of individual factors like age, gender and physical activity in determining such disorders.*

Methods: *A group of 35 voluntary urologists carrying out ultrasound scans were selected: 13 were working for the 1° Teaching Hospital Urology, 11 for the 2° Teaching Hospital Urology, 2 for the Hospitalization Urology of the Policlinico of Bari and 9 for Urology of Public Corporation Di Venere of Bari. A questionnaire, divided in two parts, was administered to the sample: the first aimed at collecting demographic data and at describing the operators' workload and the second focused on the possible presence of CTS and MSD symptoms.*

Results: *32 urologists over 35 performed more than 5 scans per week and more than 5 scans per day. On average the specialists were carrying out this activity since 18 years wheras for post-graduate students, this time was about 4 years. Twentysix subjects (74%) showed no symptoms, 8 subjects (23%) showed from 1 to 4 symptoms which can be associated to the presence of CTS; only one subject presents more than 5 symptoms. As regards MSD, 6 urologists (17%) did not present disorders, 24 subjects (69%) showed from 1 to 4 symptoms and 5 subjects (14%) presented more than 5 symptoms.*

Conclusions: *The use of US scan examination is completely safe both for the healthcare of the patients and the operator. For what concerns healthcare risks, it is highly recommended to adopt a correct posture when performing the examination and to use the provided chair.*

KEY WORDS: *Ultrasound; Carpal tunnel syndrome; Musculoskeletal disorders; Urology.*

INTRODUCTION

The ultrasound scan or echotomography is an ultrasound (US) diagnostic technique used in a routinely way in the internal medicine, surgery and radiological field. The ultrasound used, present a frequency which goes from 2 to 20 MHz. This frequency has been chosen taking into account the fact that the higher the frequency is, the better is the image resolution and the lower is the penetration in the subject. In the relevant scientific literature, studies have been reported regarding interactions among US and biological tissues; US, indeed, can cause diverse effects: a raise of the biological tissue temperature, mechanical effects with alterations in permeability of cells membranes or cavitation effects in gas-containing tissues. Negative effects on healthcare operators have not yet been documented.

US, being physical agents which can cause risks for healthcare and safety of workers, are regulated by *Article 180 of the Legislative Decree 81/08*.

American Conference of Governmental Industrial Hygienists (ACGIH) 2009 supplies for the Threshold Limit Values (TLV) as regards frequencies among 10 and 20 KHz, imposing that the TLV-Time Weight Average (TWA) is of 8 working hours between 88 and 94 dB and the TLV-Ceiling (TLV-C) is of 105 dB (1).

From the literature it can be inferred that there is a significant correlation between the presence of musculoskeletal problems – like CTS or musculoskeletal disorders (MSD) – and US scanning activity in healthcare operators.
Carpal Tunnel Syndrome (CTS) is one of the most frequent neuropathies in the industrialized world, given its correlation with particular postures of the body and, in particular, of the wrist when performing working activities. Indeed, it has been demonstrated an association between CTS and repetitive jobs, both in presence or absence of the use of particular strength in doing activities. This is because extended and/or repetitive movements of wrist flexion or extension cause an increase of internal pressure inside the carpal tunnel, determining the compression of the median nerve. A minor effect is present in case of fingers flexion. The age class mostly affected by such syndrome is that belonging to the interval 40-60 years of age, independently from gender. In 70% of the cases the pathology involves both hands (bilateral), with the major incidence on the dominant hand (2).
Traceables symptoms for CTS are pain, insensitivity, soreness, tingling to the first three hand fingers, hand and wrist pain during the night and numbness of hands when waking up.
MSD, as correctly stated in the literature, regard mainly neck and back and are correlated with several working activities, since extended static postures are requested, causing isometric muscular contractions of neck, back and superior limbs (3).
The objectives of our study are: 1) assessing if US used during US scans can represent a risk for the healthcare of operators; 2) verifying the frequency of CTS symptoms and MSD, trying to assess the possible correlation with job load and ultrasound scanning procedures; 3) assessing the role of individual factors like age, gender and physical activity in determining such disorders.

Material and methods

A group of 35 voluntary urologists who carry out US scans were selected. Of these, 13 work for the *1st Teaching Hospital Urology*, 11 work for the *2nd Teaching Hospital Urology*, 2 work for the *Hospitalization Urology of the Policlinico of Bari* and 9 work for *Urology of Public Corporation Di Venere of Bari* (Figure 1).
After having signed the informed consensus, a questionnaire, which is reported in the appendix of this work, was administered; such questionnaire has been already used in an analogous study regarding a group of U.S.A. cardiologists performing ultrasound scans; in our study the questions were adapted to urologists (4). The questionnaire was divided in two parts: the first was aimed at collecting demographic data and at describing the operator's workload; in this part we can found questions regarding age, gender, work experience, type of US scan carried out, frequency used in the exams, number of US scans performer per week and per day and the average time spent making US scans. The comfort perception coming from using the chair when carrying out the exam was also assessed. Another factor considered was the referred to physical activity: data were collected on the typology and frequency of training performed to assess possible effects on MSD.
The second part of the questionnaire was focused on the possible presence of symptoms which can be referred to CTS or to MSD.
As regards CTS, symptoms investigated were: 1) pain to the first three hand fingers, 2) insensitivity of the first three hand fingers, 3) soreness to the first three hand fingers, 4) tingling to the first three hand fingers, 5) wrist and hands pain during the night and 6) numbness of hands when waking up. As far as the MSD are concerned, the presence of the following symptoms was evacuate: 1) neck and/or back pain, 2) tingling to upper or lower limbs, 3) back and/or neck pain during the night, 4) pain when ending a working day, 5) pain when staying still, 6) pain when walking, 7) asthenia without pain, 8) back and/or neck movement reduction.

Figure 1.
Wards sub-division.

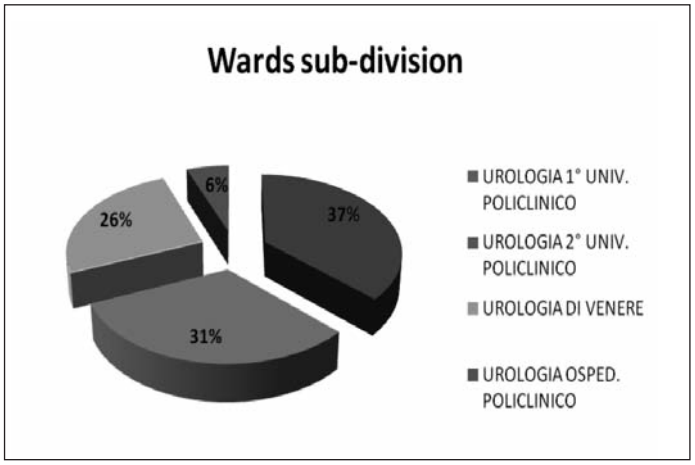
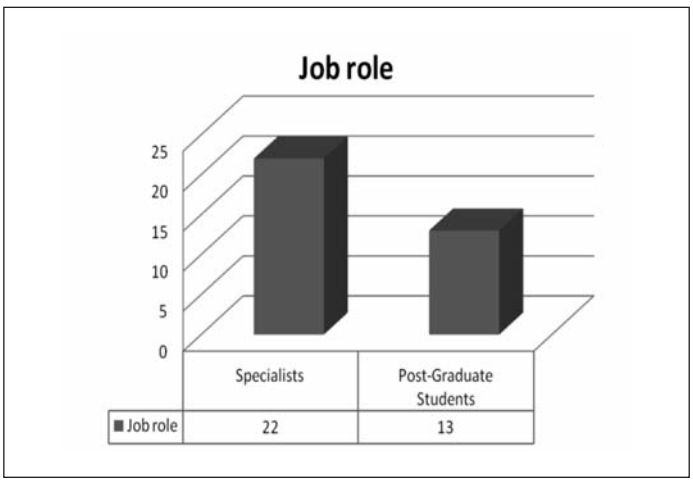


Figure 2.
Job role.



All the data collected with the questionnaire were inserted in a database with Excel 2007 and, subsequently, a descriptive analysis was carried out.

Results

The sample of doctors partecipating to the study is composed by 31 males and 4 females; the mean age of the sample is 42 years old. Of the 35 doctors, 22 are urologist specialists and 13 are post-graduate students (Figure 2). Everyone perform, by job rotation, ambulatory activity, seven days per week for six hours per day.

From ambulatory registers we have discovered that each year an average of 3500 US scans in every ward are performed, subdivided into pelvis, transrectal and Doppler US scans. These scans are performed both in ambulatory and ward environment (for check up and in emergency). Each of the probes used send out US of a variable frequency from 3,5 to 7,5 MHz, according to the type of exam carried out. The US ray emitted by the ultrasound probe is collimated and, when the US scan is in stand-by mode, it does not emit US.

The patient turnover is of about 20 minutes of which 8-10 minutes are used to carry out the US scan.

32 urologists on 35 perform more than 5 scans a week and more than 5 scans a day (Figure 3). On average the specialists carry out the US scan activity since 18 years while, for the post-graduate students, this time is about 4 years.

The main structure in which the doctors of the sample work is the public hospital; only 5 of them also work for private diagnostic structures.

70% of the doctors have answered that he/she does not dedicate more than 30% of his job shift to the US scan activity (Figure 4).

The job position is provided with a mobile and adjustable chair. Notwithstanding, 94% of the urologists does not use the chair provided and, for this reason, adopt a wrong position, staying in an upright position with the back inflected on the right (Figure 5).

54% of the doctors examined has declared not to perform physical activity; the remaining 46% practices sports for an average of about 35 minutes a day (Figure 6). The US scan probe is used with the right hand; for its characteristics it needs a three-point grip which involves the first three hand fingers, sometimes with the help of the last two fingers. The movements made during the exam are: inflection, extension, lateral inflection and clockwise/anti-clockwise wrist rotations, along with a continuous and high pressure on the wrist.

Figure 3.
Echographies per day and echographies per week.

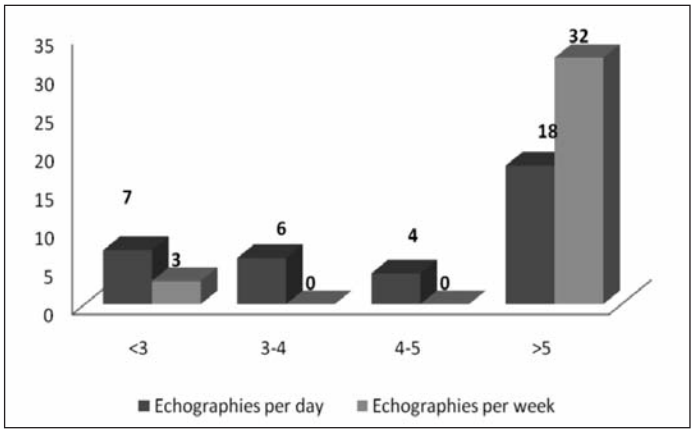


Figure 4.
Time dedicated to US scan.

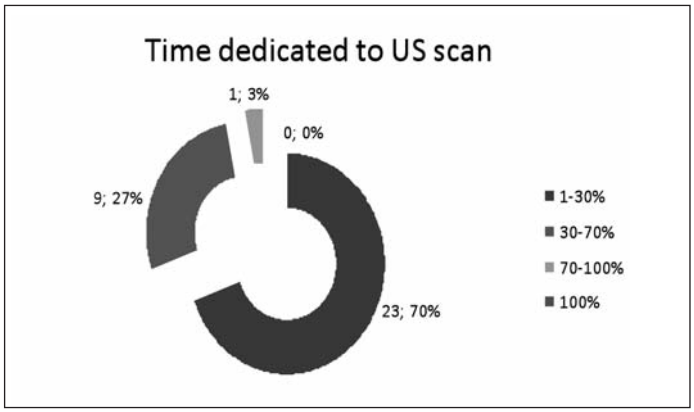


Figure 5.
Chair use.

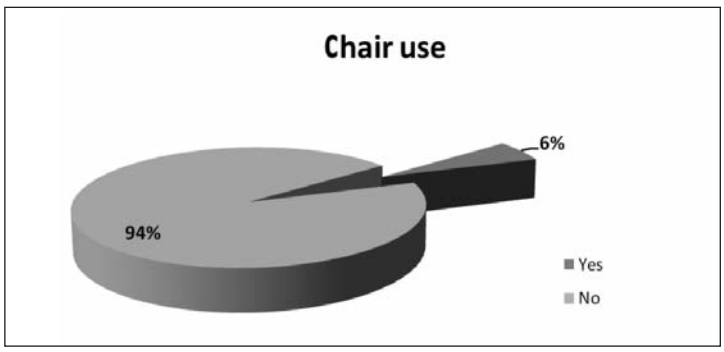


Figure 6.
Physical activity.

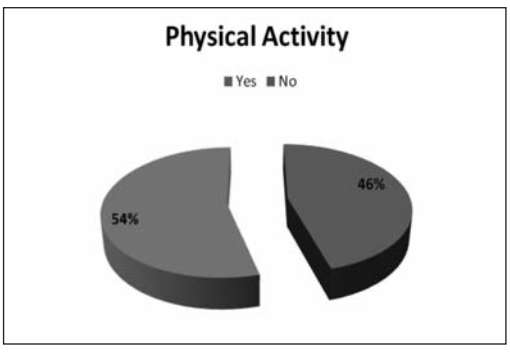


Table 1.
Three classes of symptoms for CTS and musculoskeletal disorders.

Symptoms Types	Symptoms Experienced*		
	No symptoms	Low symptoms	High symptoms
CTS symptoms	26 (74%)	8 (23%)	1 (3%)
Musculoskeletal disorders (MSD)	6 (17%)	24 (69%)	5 (14%)

*No symptoms: 0 symptoms, Low symptoms: 1-4 symptoms, High Symptoms: ≥ 5 symptoms

The symptoms regarding CTS and MSD were analyzed separately, once the data were collected; symptoms were classified into three classes: 1) no symptoms, 2) low symptoms (from 1 to 4 symptoms), 3) high symptoms (≥ 5 symptoms).
For what concerns the indicators of CTS, 26 subjects (74%) show no symptoms, covering all the age classes considered; of these, almost 33% practice sports regularly (at least 30 minutes a day).
8 subjects examined (23%), distributed in an age class from 31 to 70 years old, show from 1 to 4 symptoms which can suggest the presence of CTS; of this group, everyone carry out more than 5 scans per week and 50% does sports regularly.
Only one subject of more than fifty years of age presents more than 5 symptoms redirecting to CTS; the subject carries out more than 5 scans per week and does not make sports (Table 1-2).

As regards symptoms leading to MSD, 6 urologists (17%) do not present disorders; almost every subject belonging to this group performs more than 5 US scans per week and only 50% does sports. 24 subjects (69%) show from 1 to 4 symptoms; age does not seem to have a fundamental role in the occurrence of such disorders, since the sample is equally distributed along all the age classes. In this group also physical activity does not give us relevant information for the purposes of the study. 5 subjects (14%) present more than 5 symptoms and carry out more than 5 scans per week.
Also in this case age does not play a role, since symptoms occur along all the age classes. 1 subject over 4 (25%) belonging to this group does sports; despite this, the restricted number of observations in our sample doesn't support the hypothesis of a unique interpretation about the role of physical activity in determining the disorders (Table 1-3).

Table 2.
CTS symptoms referred to the number of US scans per week, to physical activity and to age.

	No symptoms (74%)						Low symptoms (23%)						High symptoms (3%)						Tot.
Echo/week	< 3		3-5		> 5		< 3		3-5		> 5		< 3		3-5		> 5		
Physical Activity	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	
20-30	-	2	-	-	4	-	-	-	-	-	-	-	-	-	-	-	-	-	6
31-40	-	-	-	-	5	4	-	-	-	-	3	-	-	-	-	-	-	-	12
41-50	-	-	-	-	-	5	-	-	-	-	-	1	-	-	-	-	-	-	6
51-60	1	-	-	-	2	2	-	-	-	-	-	3	-	-	-	-	-	1	9
61-70	-	-	-	-	-	1	-	-	-	-	1	-	-	-	-	-	-	-	2
Tot.	1	2	-	-	11	12		-	-	-	4	4	-	-	-	-	-	1	35

Table 3.
MSD symptoms referred to the number of US scans per week, to physical activity and to age.

	No symptoms (17%)												Low symptoms (69%)												High symptoms (14%)												Tot.
E/W	< 3				3-5				> 5				< 3				3-5				> 5				< 3				3-5				> 5				
C.U.	Y		N		Y		N		Y		N		Y		N		Y		N		Y		N		Y		N		Y		N		Y		N		
P.A.	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	
20-30	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	1	-	3	-	-	-	-	-	-	-	-	-	-	-	-	-	6
31-40	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	5	3	-	-	-	-	-	-	-	-	-	-	1	1	12
41-50	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	-	-	-	-	-	-	-	-	1	-	-		6
51-60	-	-	-	-	-	-	-	-	-	-	1	2	-	-	1	-	-	-	-	-	-	-	1	3	-	-	-	-	-	-	-	-	-	-	-	1	9
61-70	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	1	2
Tot.	-	-	-	1	-	-	-	-	-	-	3	2	-	-	1	1	-	-	-	-	1	-	10	11	-	-	-	-	-	-	-	-	1	1	3		35

*E/W: echographies/week; C.U.: chair use; PA.: physical activities; Y: yes; N:no; T: total

APPENDIX: Questionnaire

Demographic data and description of the echographist's experience

1. Age: _____ years
2. Gender: ❑ M ❑ F
3. Your ward: _____
4. Your task exercised: _____
5. From how long do you carry out US scans?_____ years
6. What kind of US scan do you effect? Write Yes or No near each sentence.
   Abdominal US scan_____ Transrectal US scan_____
   Pelvic US scan_____ Doppler ultrasound examination_____
7. Which frequencies do the US use in US scan? _____ MHz
8. How many US scans per week do you effect?
   ❑ < 3 ❑ 3-4 ❑ 4-5 ❑ > 5
9. How many US scan per day do you effect?
   ❑ < 3 ❑ 3-4 ❑ 4-5 ❑ > 5
10. How many hours a day do you use the US scan?
    ❑ < 3 ❑ 3-4 ❑ 4-5 ❑ > 5
11. How many time do you spend for each US exam?_____ minutes
12. What percentage of working activity dedicated to the US scan?
    ❑ 100% ❑ 70-100% ❑ 30-70% ❑ 1-30%
13. In which health facilities do you effect US exams?
    ❑ Public sector
    ❑ Sector operating within the National health service
    ❑ Private sector
14. Do you train? ❑ YES If yes, how many time per day?_____ minutes
    ❑ NO
15. Do you use adequate chair during the US scan? ❑ YES
    ❑ NO

Questions about possible symptoms referred to upper extremity and back

Symptoms of Carpal Tunnel Syndrome:

1) Tingling in the thumb and/or index and middle fingers	❑ YES	❑ NO
2) Numbness in the thumb and/or index and middle fingers	❑ YES	❑ NO
3) Pain in the thumb and/or index and middle fingers	❑ YES	❑ NO
4) Burning in the thumb and/or index and middle fingers	❑ YES	❑ NO
5) Numbness in hands upon awakening	❑ YES	❑ NO
6) Pain at night in wrist and/or hand	❑ YES	❑ NO
7) Clumpsy fingers	❑ YES	❑ NO

Symptoms referred to musculoskeletal disorders:

1) Pain in neck and/or back	❑ YES	❑ NO
2) Tingling and or numbness in extremity(s)	❑ YES	❑ NO
3) Pain at night in neck and/or back	❑ YES	❑ NO
4) Pain at the end of your shift work	❑ YES	❑ NO
5) Pain in standing	❑ YES	❑ NO
6) Pain in walking	❑ YES	❑ NO
7) Asthenia without pain	❑ YES	❑ NO
8) Restriction of motion in the neck and/or back	❑ YES	❑ NO

The differences among gender were not investigated, given the small number of females present in the sample.

Discussion and conclusions

Bone-joint wrist pathologies coming from work activities are present in several working categories. Numerous studies regarding operators carrying out US scans have demonstrated a significant correlation between musculoskeletal symptoms frequency, working shift length and type of scans performed. These studies have also highlighted several cases of CTS (4).

In our case study, despite it is composed by only 35 urologists, the frequency of CTS symptoms is generally low and suggests the hypothesis that for them the CTS risk due to US scan activity is low. The influence of age and daily physical activity on CTS symptoms doesn't appear. Conversely, the number of scans performer seems to have a key role, because it increases the duration of wrist inflection, and the repetitiveness of movements.

Instead, the distribution of the MSD frequency involves a large part of the sample. 20% of the doctors, indeed, pointed out MSD documented, referred to bone-degenerative pre-existing diseases, which increase the frequency of these symptoms.

The analysis of MSD in our study doesn't give information regarding a unique interpretation about the role of US scan on MSD, both because the work time occupied for this activity is limited (it doesn't exceed 30% of work time in 70% of the cases), and because in almost every cases there is an incorrect custom of not using the chair during the US scan exams.

Moreover we can't disregard that urologists usually perform surgery activities in which it is needed assuming fixed and protract positions which can weight upon the MSD frequency. Neverthereless, we can't exclude a possible synergic effect between the adoption of inadequate posture during the US scan activity and the fixed and protracted positions during the activity of operating room.

In conclusion, if we come back to our purposes of this preliminary study, it can be notice a how the use of US scan exam is completely safe both for the healthcare of the patients and that of the operator. This is because exposition levels are sharply lower than the limits imposed by ACGIH; moreover, the collimated ray, the time used for each exam and respect of pauses among exams make the possible bio-effects of US not relevant, despite their daily use (1).

For what concerns healthcare risks, it is highly recommended to adopt a correct posture when performing the exam and to use the provided chair. These recommendations are fundamental for avoiding the occurrence or the worsening of MSD. In addition to this, it can be suggested to undertake daily physical activity in order to better the trophism and neck/back muscular elasticity.

We are currently deepening our study, administering the questionnaire also to the medical staff of other wards in order to widen case records.

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PRESENTATION

Contrast enhanced ultrasound of renal diseases.

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Summary

With the advent of microbubble contrast agents and contrast-specific techniques, contrast enhanced ultrasonography (CEUS) has become a powerful additional tool for radiological imaging. When microbubbles are administered intravenously, the sensitivity and specificity of ultrasound (US) can approach those of computed tomography (CT) and magnetice resonance (MR) with the advantages of no radiation, lower cost and the possibility of their use in patients with renal failure or in intensive care units. Functional (perfusional) information can be obtained in addition to morphologic information, often making further imaging unnecessary. Nevertheless, CEUS requires expertise and adequate US equipment. In addition, subjects and organs unsuitable for US are also unsuitable for CEUS, which is not a panoramic imaging modality and consequently not a substitute for comprehensive whole-body imaging.

KEY WORDS: *Contrast-enhanced ultrtasonography (CEUS); Renal diseases.*

INTRODUCTION

Ultrasound contrast agents (UCAs) have been introduced relatively recently. They consist of microbubbles that are able to resonate in the ultrasonography beam and change the backscattered wave resulting in both an enhancement and a change in the waveform.
Contrast-enhanced ultrasonography (CEUS) requires contrast-specific software, suppressing the static signal from background tissues and highlighting the signal from circulating microbubbles. Exam is acquired in real-time, like a normal grey-scale investigation. A colour-scale is now used for a more detailed visualization.
UCAs are intravascular ("blood pool") substances, lacking an interstitial spread; their half-life in blood is typically a few minutes [1, 2]. Because of the lack of an extravascular diffusion, UCAs theoretically fit perfectly as functional traces of organ circulation.
UCAs are flexible and well-tolerated tools, and serious reactions are rarely reported [3]. Nevertheless, allergy toward contrast medium constituents or other addicted substances should always be considered. Starving or preliminary laboratory testing are not required. UCAs volume is usually 2,4 ml, followed by 5 ml of saline; it can also be repeated, to evaluate the arterial-phase behaviour of more organs (e.g. both kidney for trauma evaluation) or for evaluating more lesions.
UCAs do not usually allow the rescue of a non-diagnostic US examination. Difficult patients, such as those who are meteoric, are also difficult to scan with CEUS. The need for adequate training of the operator should be considered. In addition, CEUS requires scanners fitted with specific software.
CEUS should be intended first as a completion of US examination, which provides additional data not achievable with baseline US. Secondarily, to improve an inconclusive US examination, CEUS can act as a problem-solving modality.

KIDNEY

CEUS of the kidney is an emerging field for UCAs. Microbubbles can be injected without regard for renal function, and the intense enhancement of the renal parenchyma makes it easy to detect hypoperfused lesions such as infarctions or haemorrhages. The kidneys show a rapid, intense, and transient (as a consequence of lacking glomerular filtration) enhancement after IV UCA injection (Figure 1).
The arterial phase of CEUS starts at the moment of arrival of microbubbles within the arterial pedicle of the scanned organ (10-15 seconds after intravenous [IV] injection) and lasts up to about 40 seconds, when the venous phase becomes prevalent. The venous and late phase lasts from 3 to 6 minutes, depending on the scanned parenchyma. Because there is no renal excretion, UCAs can be safely employed in patients with acute or chronic renal insufficiency.

Figure 1.

Normal kidney at CEUS. After UCA administration renal parenchyma shows a homogeneous enhancement with the exclusion of the papillae which are normally avascular.

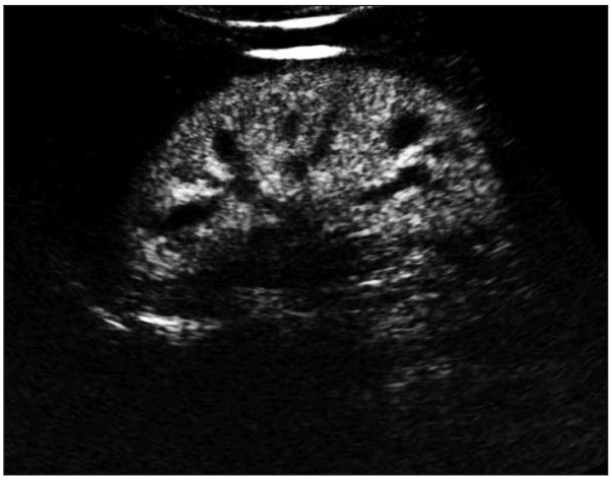
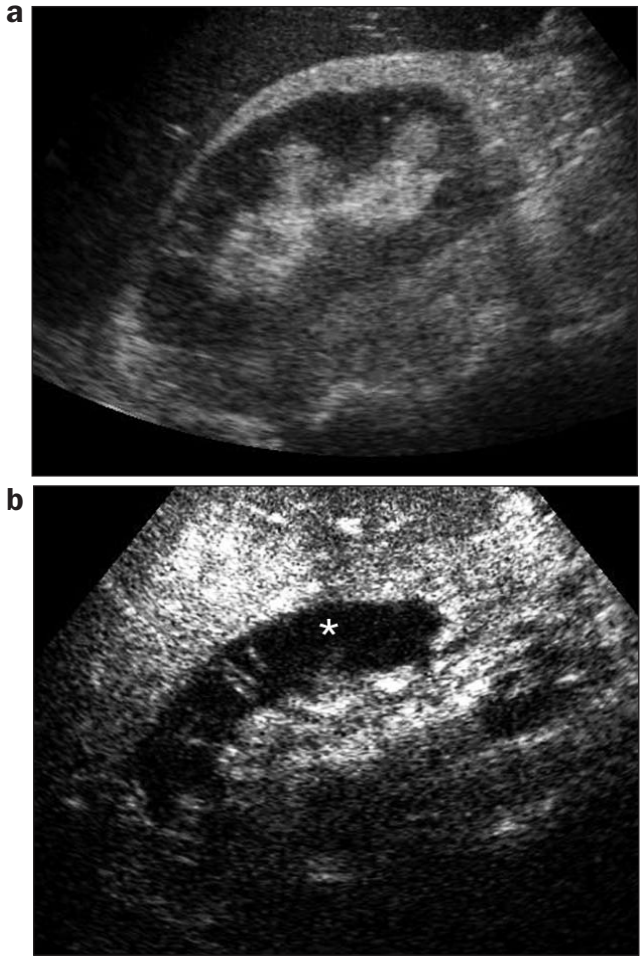


Figure 2.

Patient with acute right pain. Longitudinal scan on the right kidney (a) and CEUS (b). Gray-scale sonography shows a normal appearing kidney, with no dilatation of the escretory system (a). Color-Doppler (not shown) was not diagnostic. CEUS (b) shows lack of contrast enhancement of the parenchyma, due to extensive renal ischemia (*).



Renal ischemia

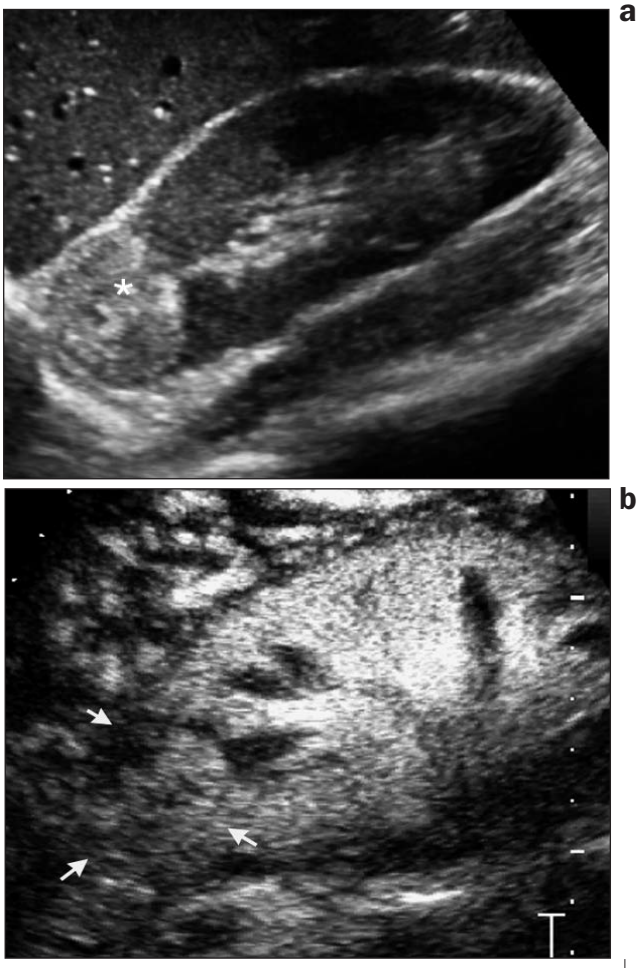
Color-Doppler US is the first-line imaging modality to detect renal perfusion defects but it has clear limitations because of reduced sensitivity to low-velocity and low-amplitude flows. CEUS has been proposed to overcome these limitations and was found effective for depicting focal renal perfusion defects initially in experimental studies [4-6]. Recently various investigators have showed an excellent diagnostic performance in the detection of renal ischemia approaching that of contrast enhanced CT [7]. Moreover, the excellent spatial resolution of CEUS allows an effective differential diagnosis between renal infarction and acute cortical necrosis, which appears as nonenhancing cortical areas with preserved hilar vascularity (Figure 2).

Solid renal lesions and pseudotumors

After microbubble injection solid renal tumors show diffuse, homogeneous or heterogeneous contrast enhancement during the early corticomedullary phase, often with a hypervascular appearance, and have a variable contrast enhancement in the remaining phases, generally similar

Figure 3.

Renal tumour (*) at the upper pole of the right kidney (a) studied with CEUS (b). A well defined expansive, hyperechoic mass is observed with intense and not homogeneous enhancement (arrows).

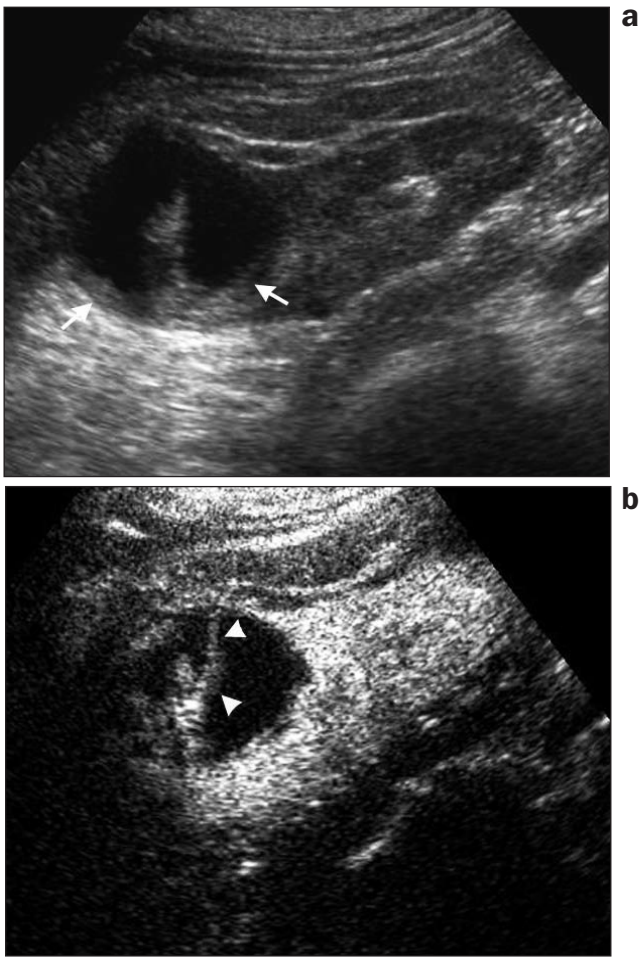


to normal renal parenchyma [8-10]. The enhancement is limited to the solid viable regions, sparing intratumoral avascular necrotic, hemorrhagic, or cystic components. Some lesions, usually papillary or chromophobe tumors but also metastases and approximately 13% of clear cell carcinomas, enhance less than the surrounding parenchyma in all vascular phases (Figure 3).
Because enhancement of many renal tumors is similar to that of renal parenchyma in most vascular phases, the detection rate of small tumors is unlikely to be much improved by contrast injection.
Ascenti et al. [11] suggest that CEUS is effective for visualizing the tumor pseudocapsule, which appears after microbubble injection as a rim of perilesional enhancement increasing in the late phase of the examination.
Whatever the degree of vascularization, the vascular pattern of renal tumors is different from that of renal parenchyma. This difference could be helpful for differentiating normal renal variants from real focal lesions [9, 13].
Preliminary investigations suggest that CEUS is more sensitive than contrast-enhanced CT in detecting blood flow in hypovascularized lesions [9, 12]. Tamai and colleagues [14] demonstrated enhancement in 5 hypovascular renal tumors with an equivocal enhancement on contrast-enhanced CT. Presence of wall calcification limit interrogation of the solid lesion, resulting in an important limitations of CEUS for a fully evaluation of the mass.

Cystic renal lesions

The sensitivity of CEUS in detecting flow in hypovascular renal lesions allows an adequate differential diagnosis between simple cysts and atypical cystic masses. It allows characterization of renal cystic lesions as benign or malignant with at least the same diagnostic accuracy as contrast-enhanced CT [9, 10, 15] (Figure 4).
Quaia et al. [16] analyzed a series of 40 consecutive complex cystic renal masses finding an overall diagnostic accuracy of CEUS better than CT in the diagnosis of malignancy. In particular, CEUS was more sensitive than CT in detecting enhancement of the cystic wall, septa, and solid components.
Park et al. [10] evaluated with CT and CEUS 31 pathologically confirmed cystic renal masses using the Bosniak classification. The diagnostic accuracies of CEUS and CT for malignancy were 74% and 90%, respectively. In 26% of lesions there were differences in the Bosniak score that were upgraded by CEUS. Moreover, for 6 lesions, solid components were detected by CEUS but not by CT.
Ascenti et al. [17] compared prospectively 40 consecutive cystic renal masses with CEUS and CT using the Bosniak system criteria. For CEUS and CT, the interobserver agreement was high, and a complete concordance was observed between CEUS and CT in the differentiation of surgical and nonsurgical cysts. CEUS should be used to characterize renal masses with a complex cystic appearance, provided that the lesion can be explored adequately. CT is still necessary for staging purposes. Because of its availability and its lack of ionizing radiation CEUS is well suited for follow-up of nonsurgical lesions or in the follow-up of renal masses.

Figure 4.
Complex cyst at the upper pole of the left kidney. Longitudinal scan (a) shows complex cystic lesion (arrows) with a thick septum. After UCA administration (b) there is an evident contrast enhancement of the septum (arrowheads) giving diagnosis of Category III atypical cystic mass according to Bosniak classification.

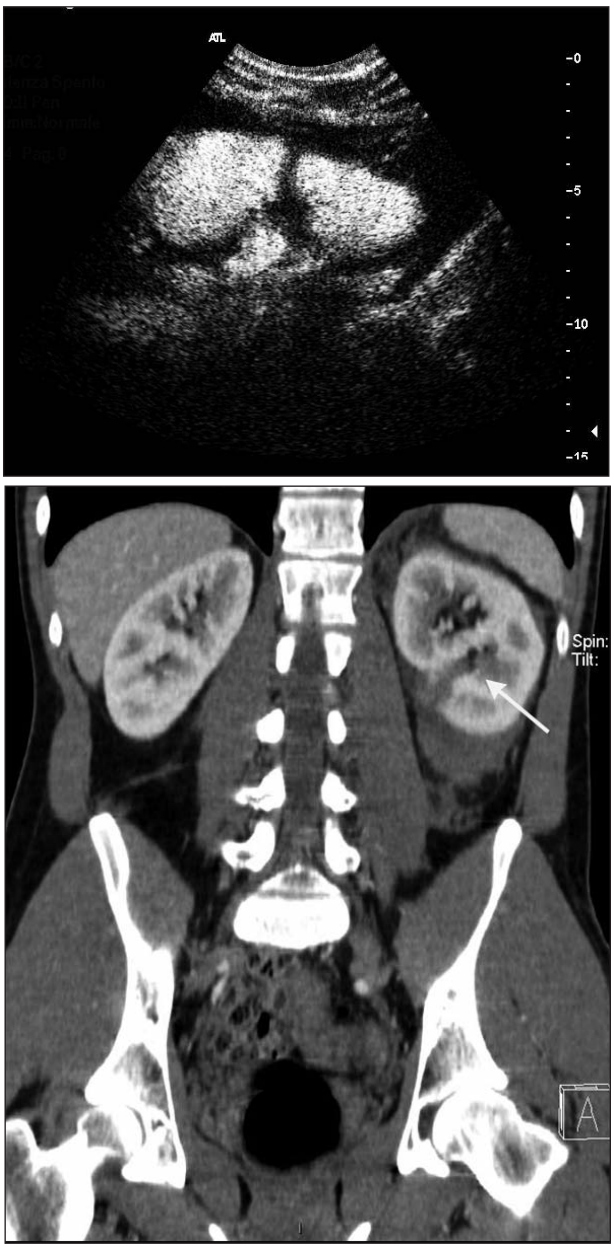


Renal trauma

Renal injuries present as defects of vascularization in a wellperfused parenchyma after microbubble administration (Figure 5).
Every interruption of the renal profile is consistent with a capsular laceration. Renal artery tear or thrombosis presents with absence of parenchymal perfusion. Focal UCA extravasation suggests active hemorrhage. Although UCA injection improves the sensitivity of US for identification of renal injuries, the role of this technique in the clinical practice is debatable. Injury to the renal collecting system may be overlooked at CEUS because of a lack of microbubbles urinary excretion [12]. In addition, severe trauma patients, even although hemodynamically stable, usually require a panoramic evaluation with CT of all abdominal organs. CEUS could replace or integrate US in the triage of hemodynamically stable patients with minor abdominal traumas. However, *Poletti et al.* [18] found that even in optimal conditions solid organ injuries may be missed. Differently, in our experience we did not miss major renal injury [19]. Small and lowgrade injuries may be occasionally over-

Figure 5.

Renal trauma with parenchymal rupture. CEUS (a) and CT-Urography (b). Patient with minor renal trauma with hematuria and left flank pain and negative gray-scale sonography. The contrast administration allows to detect a complete capsular and parenchymal laceration, but do not allow to visualize caliceal tears. The following CT confirmed a simple parenchimal rupture with hematoma (arrow) but no extravasation of contrast medium (b).



looked, especially in obese patients, and when perirenal hematoma is small or absent. Moreover, CEUS can be successfully employed in the follow-up of minor renal injuries that are managed conservatively to reduce the use of CT especially in children and young adults.

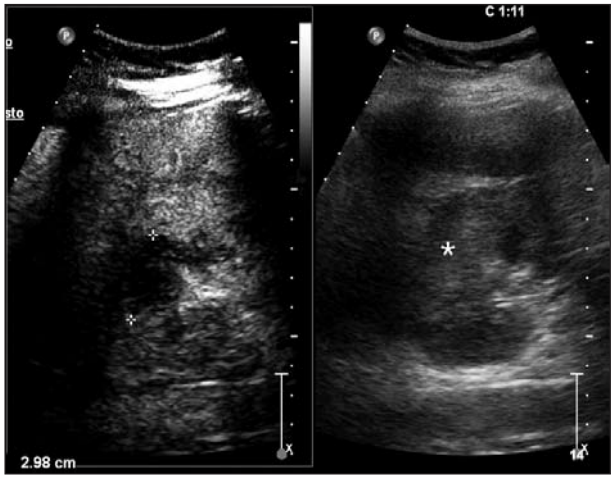
Renal infections

Renal abscesses are depicted effectively after UCA injection, because they do not present with intralesional vessels, which are destroyed or displaced by the inflammatory process (Figure 6).

Focal acute pyelonephritis may improve in noticeability after microbubble injection if renal vessels are compressed by the adjacent oedema, revealing hypoperfused areas [8]. *Mitterberger et al.* [20] evaluated prospectively 100 consecutive patients with clinical symptoms suggestive of acute pyelonephritis and showed that CEUS and CT are almost equally sensitive and specific for detecting renal changes.

Figure 6.

Acute renal pyelonephritis. Site-to-site image which allows to follow in real-time the native image on the right side and the contrast enhancement on the left side. Gray scale image shows a normal appearing kidney with limited hyperecohic area (*). After CEUS a cortical perfusion defect compared to the normal adjacent parenchyma.



CEUS and tumour renal ablation

Minimal approach of small renal tumours is now widely recognized as the reference technique for treatment. Radiofrequency ablation (RFA) are cryoablation are the preferred procedures for these cases. RFA is performed percutaneously, whereas cryoablation is mainly performed laparoscopically; both are valuable alternative to nephron-sparing surgery [21]. RFA can be also performed in patients with renal masses who are not candidates for surgery.

CEUS plays a key role at each step of renal tumour management using RFA and cryoablation. It improves the depiction of normal renal blood flow and tumour vascularity with high temporal and spatial resolution. During procedures, CEUS plays a key role in optimizing electrode placement, particularly when the lesion is small and poorly seen with conventional US. Finally, CEUS plays a critical role in the treatment of persisting tumour tissue (residual tumour following procedures or tumour recurrence) after the previous ablation session. Preliminary investigation suggests that CEUS can be useful in detecting residual tumour after ablation. *Meloni et al.* [22] evaluated with CEUS and CT or MRI 29 patients with 30 renal tumours before and after RFA. They found that in hypervascular tumour, the accuracy of CEUS in the detection of focal areas of tumour recurrence or pro-

gression is similar to that of CT or MRI. Recently, Correas et al reported their experience in a exhaustive review [23].

Transplanted kidney

The use of UCAs has potential to diagnose acute kidney graft rejection in its early stages. *Fischer et al.* [24] found a delayed enhancement of the renal cortex in patients with graft rejection.

This finding, however, was also observed in patients with large perirenal hematomas. Another preliminary investigation showed that in acute tubular necrosis the cortical/medullary ratio of the renal blood volume and mean transit time were significantly lower compared with the control group [25]. Perfusion defects in the renal cortex can be easily demonstrated by contrast-enhanced examination (Figure 7).

The impact of detecting these hemodynamic changes in the management of patients with non-functioning transplanted kidney could be of great impact in the management of these patients.

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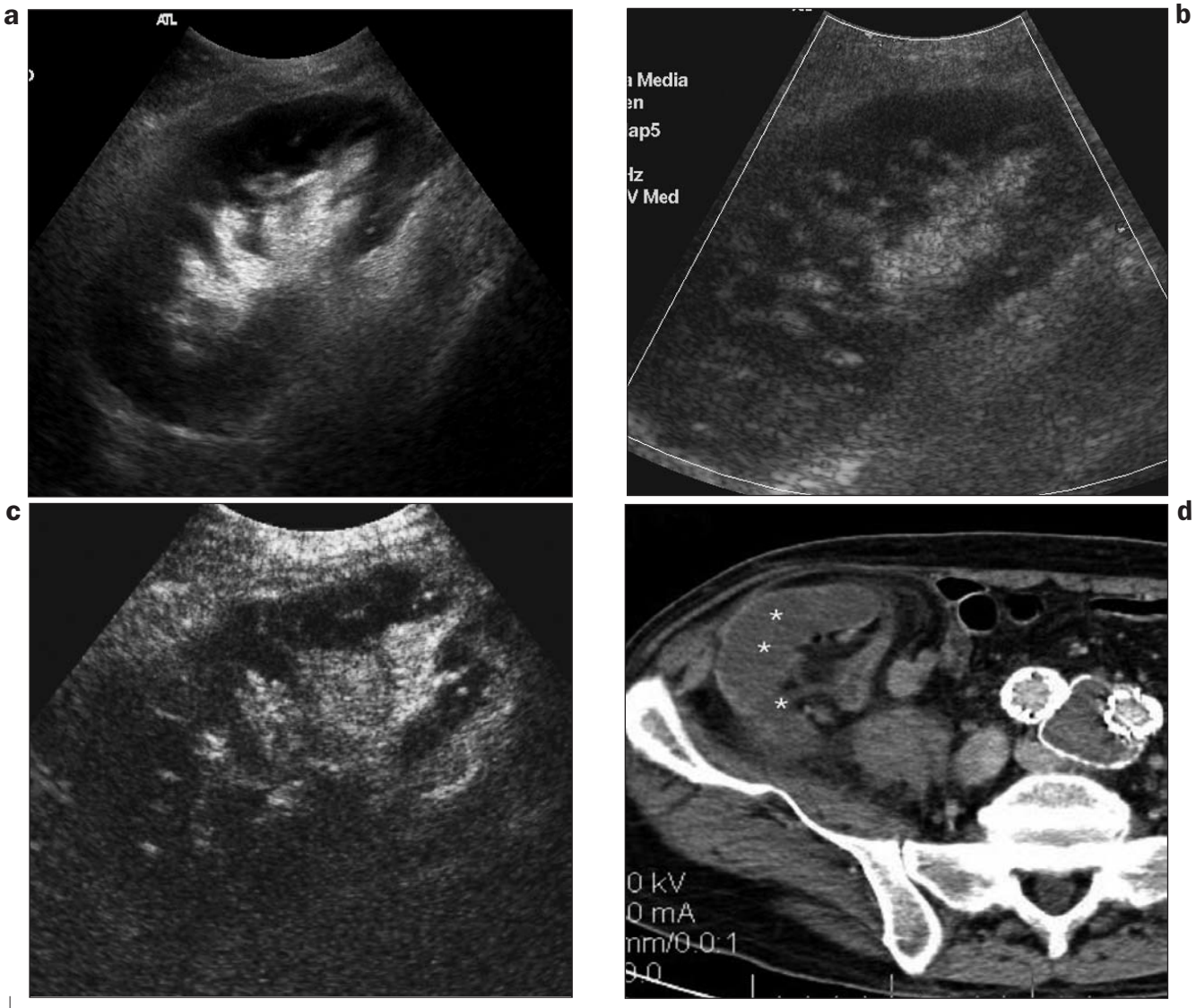
Figure 7.

Transplanted kidney with acute diffuse ischemia secondary to arterial occlusion. Gray-scale scan (a) shows a normal appearing kidney with mild hypoechoic cortex. Color-Doppler imaging does not depict any vascular structure at the level of the sinus and parenchyma (b). CEUS (c) shows absence of enhancement in the renal parenchyma and the main renal vessels. CT with contrast administration (d) confirms a complete absence of renal parenchymal perfusion (*) secondary to renal artery thrombosis.



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PRESENTATION

A retrospective study to reduce prostate biopsy cores by a real time interactive tool.

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Summary

Objective: *Prostate carcinoma (PCa) is one of the most frequent neoplasms, with more than 110.000 new cases/year in Europe. As PCa is not clearly demonstrable at transrectal ultrasound (TRUS), guidelines on TRUS guided biopsy suggest to perform a random tissue sampling (at least 8-12 "cores" depending on gland volume). Although accuracy grows with core number, patient discomfort and adverse event probability grow as well. Thus it would be worth to aim to reduce the number of prostate biopsy cores without loss of diagnostic accuracy.*

Materials and Methods: *A retrospective study was performed to evaluate the feasibility of an improved version of a rtCAB tool developed at DEIS (University of Bologna) for the reduction of prostate biopsy cores. rtCAB is an innovative processing technique which enhances TRUS video stream by a live false color overlay image that helps the physician to perform the biopsy by guiding the sampling into target zones. In order to train rtCAB, a monocentric, single operator prostate gland adenocarcinoma database has been built. The database enlists 81 patients, for a total of 743 prostate byoptic (PBx) cores and 14860 ROI. For each patient we collected age, PSA levels, digital rectal examination (DRE) findings, presence or absence of focal lesions, and prostate volume. During TRUS, raw ultrasound data were acquired and associated to each PBx core. For each core we collected both the radio frequency (RF) signal and the histological outcome.*

Results: *The whole system was optimized for reducing the number of false positives while preserving an acceptable number of false negatives. Comparing to a classical PBx approach (8-12 cores), the estimated positive predictive value (PPV) of our method increased from 25% to 40%, with an overall sensitivity of 85%.*

Conclusions: *Preliminary results show that the proposed tool can provide real-time feedback to the operator during TRUS. Sensitivity and PPV values suggest that a reduction of almost 50% the number of biopsy cores without losing in diagnostic accuracy is feasible. A prospective study is needed to further confirm these preliminary retrospective results.*

KEY WORDS: *Humans; Male; Retrospective Studies; Prostatic Neoplasms/pathology; Prostatic Neoplasms/ultrasonography.*

INTRODUCTION

Prostate carcinoma is the first most common cancer in men with a worldwide incidence of 253 cases per million of patients. Large differences can be spotted between countries [1], with Northern America, Australia and Western Europe leading in incidence and Caribbean, Southern Africa and Middle Africa leading in mortality.

Despite there is an increase in evidence that oxidative damage, dietary, environmental and predisposing genetic factors may play a role in pre-malignant PCa stages, the exact changes between a normal gland and a neoplastic one are not known yet [2].

Although this pathology tends to progress slowly, an

absolute prediction of when a localized cancer will start spreading up and causing significant problems is also not well understood; furthermore, the rate of growth and spread is strongly related to the Gleason grade [3, 4].
In order to early detect PCa, the main diagnostic tools available to the urologist include DRE, serum concentration of PSA and TRUS [5, 6]. All these procedures are non invasive and can be performed in an ambulatory environment [7, 8].
Unfortunately, PCa features at ultrasound is not always the same and the lesion is capable to be isoechoic with respect to the surrounding tissue. Thus, the main role of standard TRUS is to directly guide biopsies in order to perform a systematic gland tissue sampling. Lesion-guided biopsy can be also performed when evidence arise from DRE, PSA and ultrasonic appearance. Featuring a low risk of complications, if antibiotic prophylaxis is used [9], TRUS guided biopsy (8-12 cores) has become the standard procedure for extracting tissue samples.
As patient discomfort as well as the probability of adverse event grows along with the number cores, it is thus desirable to reduce the number of unnecessary PBx.
This work describes a retrospective study conducted at University of Bologna by the joint units of Department of Urology and Department of Electronics, Computer Sciences and Systems concerning the feasibility of innovative rtCAB tools to guide prostate biopsy by enhancing TRUS video stream.

Material and methods

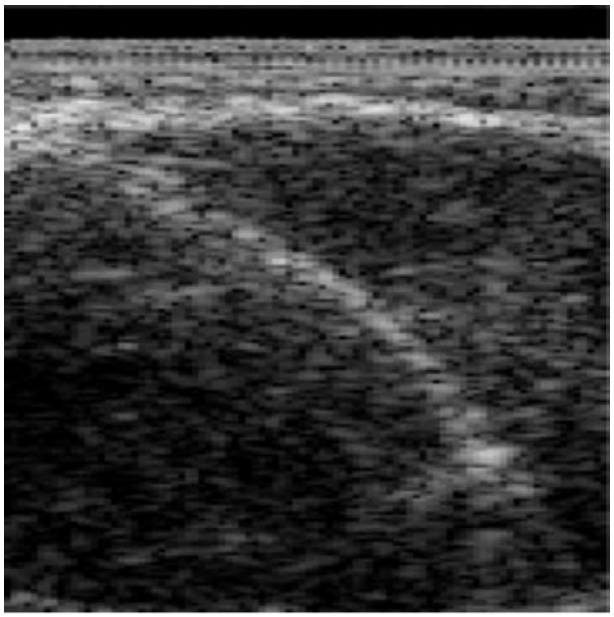
In this study, a group of 81 patients were submitted to a routinely systematic prostate gland biopsy (8-12 cores) for PCa suspect. Biopsies were performed by the same operator. During each examination the same TGC profile, impulse bandwidth, acquisition gain, aperture angle maximum depth and focal depth were set in order to standardize acquisition conditions.
For each patient the following parameters were collected before biopsy:

a. Age
b. PSA levels
c. Presence/absence of palpable lesions at DRE
d. Prostate gland volume
e. Presence/absence of focal lesions at TRUS

During TRUS, the incoming radiofrequency ultrasound raw signal was extracted from the ultrasonographer (*TECHNOS Esaote S.p.A.*) through a 1 Gbit/s optical fiber link and recorded on disk by means of *FEMMINA*, an hardware and software platform dedicated to ultrasonic signal and image processing [10]. RF data were acquired before, during and after each bioptic core extraction. A unique alphanumeric code was assigned to each core and its corresponding recording. Each core was then examined by expert pathologists and the following parameters were collected:

f. Position relative to prostate gland
g. Histological classification
h. Presence/absence of neoplastic lesions
i. Total volume of neoplastic lesions
j. Gleason score
k. Core length

Figure 1a.
Bright hyperechoic linear structure due to needle insertion.



As results, 22 patients over 81 had at least one PCa positive core, with Gleason score varying between 6 and 10 and a tumor volume between 1% and 95% of the core.
At the same time, RF data were processed as follows. First of all, frames were manually scanned looking for needle insertion: needle usually appeared as bright hyperechoic linear structure as shown in Figure 1a. Once the needle presence was verified, needle was segmented and its penetration track extracted as shown in Figure 1b. Next maximum penetration depth and prostate

Figure 1b.
Needle penetration track (black) and segmentation (white).

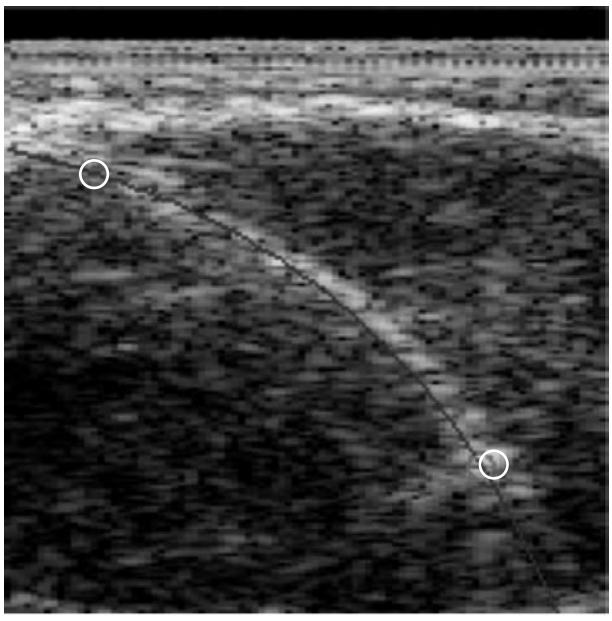
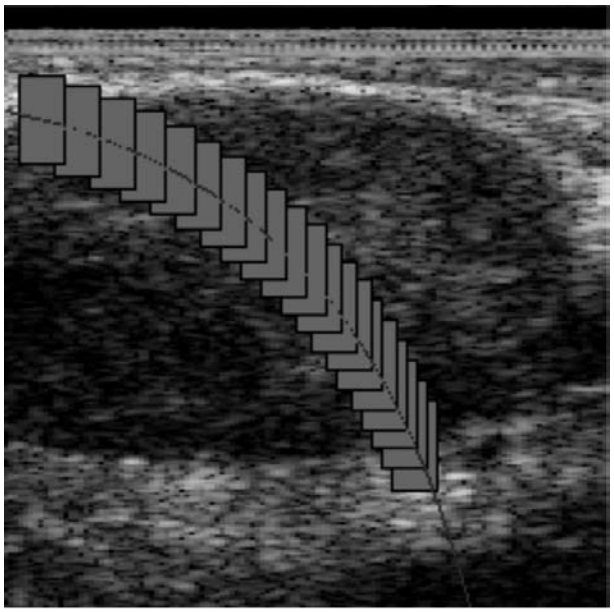


Figure 1c.
ROI superimposed to segmented needle.



gland capsule insertion point were manually detected and equispaced and partially superimposed ROI were defined as shown in Figure 1c. Finally, corresponding RF data were extracted from the three frames preceding needle insertion and associated to corresponding core. Up to 20 ROI were selected for each core. A total of 743 PBx cores and 14860 ROI were collected following this procedure.
Basing on these data an rtCAB tool [11] was trained to recognize in real-time pathological tissues by only processing RF ultrasound raw signal. To do so, an accurate and fast envelope detection algorithm is applied to the signal and the resulting image is split into Regions of Interest (ROI). Statistical parameters were estimated with an original Maximum Likelihood estimator. Finally, a non-linear supervised classification model was used to discriminate among PCa risk levels. Images created from the elaborated signals were overlayed to the TRUS images.
The rtCAB training consisted of different phases. First of all, tissue cores were subdivided into differently coded categories as shown in Table 1, depending on histological classification, total volume of neoplastic lesion and overall gland condition. Then discrimination between pathological and non pathological cores – i.e. no PCa, ASAP or high grade PIN was performed. In particular, M cores along with BB were chosen for model selection and training purposes, while all other cores were used during the different test phases.
Eighteen different models were trained on 200 database subsets of 15 M + 15 BB cores and tested versus a fixed set of 8 M + 8 BB. Both training and testing were ROI based and used a total of 600 training and 320 testing samples; these proportions were taken in order to minimize validation and training error [12, 13]. Selection of the M cores was patient based: cores from a patient in the training set were never included into the testing set. The number of patients in the test set was maximized by including only patients with no more than two pathological cores.

Table 1.
Core categories coding scheme used for training and testing.

CODE	Description
M	PCa, volume >= 70%
UM	PCa, volume < 70%
U	High grade PIN and ASAP
BB	Normal tissue from normal glands
BB*	Other tissues from normal glands
BM	Normal tissue from malignant glands
BM*	Other tissues from malignant glands

Results

In order to evaluate the effect of this innovative tool to reduce the number PBx cores necessary for correctly diagnosing a PCa, after the first model selection and training phase, the PPV was estimated for both the rtCAB and standard TRUS guided biopsy. Called 'p0' the PPV of the TRUS guided PBx, i.e. the probability of PCa positiveness of a single core extracted through standard TRUS guided PBx from a pathological gland, the probability of correctly diagnosing PCa after extracting 'N' cores, can be computed as $1–(1–p0)^N$. In order to obtain the same diagnostic value with a lower core number, the PPV (p1) of rtCAB in guiding biopsies must be higher than p0.
To detect the highest number of pathological lesions in the gland, the rtCAB threshold was optimized to maximize both PPV and sensitivity.
Slightly more than 200 cores were necessary to correctly diagnose the 22 PCa positive patients in the database, resulting in a p0 of 23.61%. A proper training of the rtCAB tool threshold and the definition of positive core by the presence of at least one positive ROI, both determined a p1 of 38.89% and were able to identify all the cores in which PCa was present. Consequently, following the results of this study, no more than 7 cores should be needed to achieve the same diagnostic value of a standard TRUS guided biopsy (8-12 cores). This trained tool (rtCAB), was also used to examine the collected RF data recordings (some results are show in Figures 2a-b).

Discussion

Preliminar numerical results obtained after training rtCAB were good. Both PPV and sensitivity are high enough to provide a significant reduction in PBx core number without a negative impact on diagnostic accuracy. Visual results on real-time processing RF data are also encouraging showing a good correspondence with histological findings.
A perspective study to demonstrate the role rtCAB in guiding prostate biopsy is needed in order to confirm these preliminary retrospective results. The future investigations should also include a larger patient database in

Figure 2a.
Example of unnecessary sampled prostatic core. Bioptic needle (white) crossed areas which were predicted to be healthy. Histological observation reported Benign prostatic tissue.

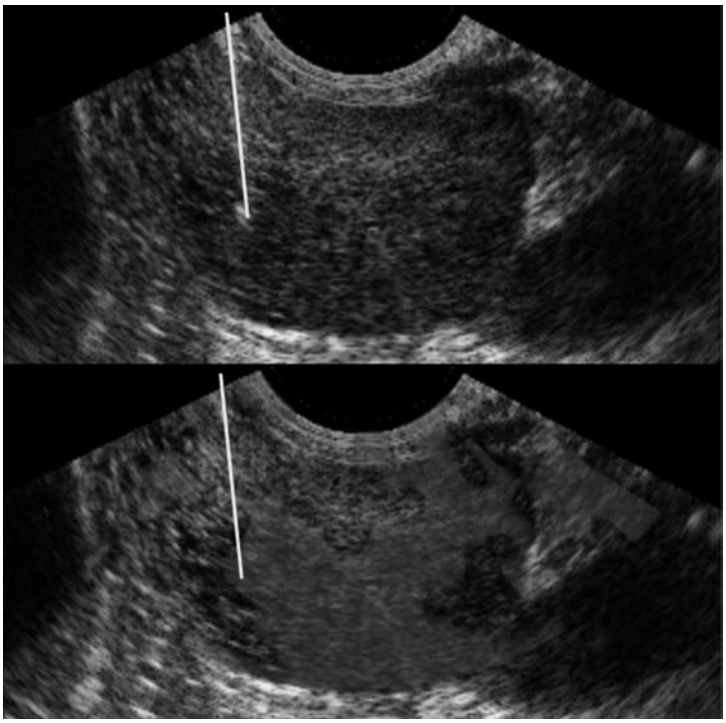
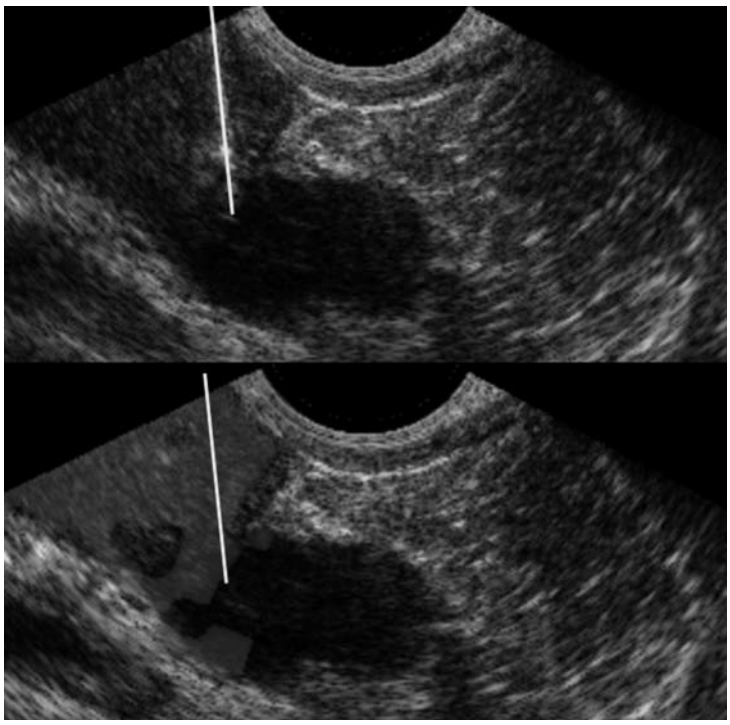


Figure 2b.
Example of correctly sampled prostatic core. Bioptic needle (white) crossed areas which were predicted to be unhealthy. Histological observation reported adenocarcinoma over 80% of core volume.



order to guarantee a more robust training phase and improve PCa detection rate. Hence other already collected parameters like age, PSA levels and gland volume could be used in conjunction with rtCAB to improve the predictive value.

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PRESENTATION

Diagnosis of high-grade prostatic intraepithelial neoplasia: The impact of the number of biopsy cores at initial sampling on cancer detection after a saturation re-biopsy.

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Summary

Objectives: To evaluate factors that may predict prostate cancer (PCa) detection after initial diagnosis of high-grade prostatic intraepithelial neoplasia (HGPIN) on 6-24 cores prostatic biopsies (PBx).

Material and Methods: We retrospectively evaluated 193 patients submitted from 1998 to 2007 to prostate re-biopsy after initial HGPIN diagnosis in three urologic departments. HGPIN diagnosis was obtained on initial systematic PBx with 6 to 24 random cores. All patients were re-biopsied with a "saturation" PBx with 18-26 cores with a median time to re-biopsy of 12 months. All slides were reviewed by expert uro-pathologists.

Results: Plurifocal HGPIN (pHGPIN) was found in 103 patients and monofocal HGPIN (mHGPIN) in 90. Seventy-two and 121 patients were submitted to > 12-core initial biopsy and ≤ 12-core, respectively. Overall PCa detection at re-biopsy was 28.4%. PSA (6.7 vs 8.5 ng/ml; p = 0.029) and age (64 vs 68 years; p = 0.005) were significantly higher in patients with PCa at re-biopsy. PCa detection was significantly higher in patients who underwent a ≤ 12-core initial PBx than in those with > 12-core (35.5% vs 16.8%; p = 0.03), and in patients with pHGPIN than in those with mHGPIN (34.9% vs 21%; p = 0.035). At multivariable analysis, PSA value (p = 0.007; HR:1.18), prostate volume (p = 0.01; HR:0.966), age (p < 0.001; HR:1.15), pHGPIN (p = 0.003; HR:2.97) and ≤ 12-core initial biopsy (p = 0.012; HR:3.62) were independent predictors of PC detection. We further analysed the 2 groups of patients submitted to ≤ 12-core and > 12-core initial PBx. Plurifocal HGPIN and older age at biopsy were independent predictors in patients with ≤ 12-core initial PBx. On the contrary, in patients with > 12-core initial biopsy, higher PSA values and lower prostate volume were independent predictors of PC detection.

Conclusions: PCa detection on saturation re-biopsy after initial diagnosis of HGPIN is significantly higher in patients submitted to ≤ 12-core than those submitted to > 12-core initial PBx. In patients with ≤ 12-core initial biopsy pHGPIN and older age were predictors of PCa detection at re-biopsy. In patients with > 12-core initial biopsy, higher PSA values and lower prostate volume was associated to an increased risk of PCa detection at re-biopsy.

KEY WORDS: *Prostatic intraepithelial neoplasia; Biopsy; Prostate cancer.*

INTRODUCTION

High-grade prostatic intraepithelial neoplasia (HGPIN) has been traditionally considered as a precursor of prostate cancer (PCa) (1-3). Transrectal Ultrasound (TRUS)-guided needle biopsies, performed because of an elevated PSA or an abnormal digital rectal examination (DRE), detected HGPIN in 4-25% of patients (4-6). Older studies show a 22% to 100% cancer detection rate on repeat biopsy in patients with an initial HGPIN diagnosis (7-8).

Several clinical variables, such as abnormal digital rectal examination (DRE), abnormal TRUS, patient age, PSA and HGPIN focality have been investigated as markers to predict the presence of PCa on a re-biopsy, but no consensus has yet been reached (9-12).
Moreover, the prognostic value of HGPIN in prostate biopsy cores has been recently questioned because several studies have shown a lower cancer yield on repeat biopsy, especially when the first sampling is performed using an extended biopsy technique (12-15).
The aim of our study was to evaluate the impact of the number of cores taken at initial biopsy on subsequent PCa diagnosis, in patients with initial diagnosis of isolated HGPIN. Furthermore, we investigated which factors may predict the risk of PCa detection at re-biopsy in these subset of patients.

Materials and methods

We retrospectively evaluated 201 patients submitted from 1998 to 2007 to prostate re-biopsy after initial HGPIN diagnosis in three urologic departments. HGPIN diagnosis was obtained on initial systematic TRUS prostate biopsy (PBx) with 6 to 24 random cores (median: 12 cores). All patients were re-biopsied with a saturation PBx with18-26 cores (mean 22 cores; median 20 cores) with a median time to re-biopsy of 12 months (range: 3-30 months), on the basis of the personal urologist's opinion.
All slides were reviewed by expert uro-pathologists. Eight patients were excluded: a concomitant atypical small acinar proliferation (ASAP) in 6 cases and a concomitant CaP micro-focus in two cases.
Information on PSA and PSA density (PSAD) values at biopsy time, patient age, DRE or TRUS results, number of cores with HGPIN, time interval between initial and repeat biopsy, and PCa characteristics on needle biopsy were retrospectively assessed from combined data-base from the three centers.
The HGPIN was classified as pluri-focal when neoplastic foci were present in ≥ 2 cores.
When patients with initial HGPIN diagnosis underwent re-biopsy, 3 diagnoses were made: benign prostate tissue, HGPIN or CaP. We combined the first two findings in a "no-cancer" group in order to perform univariable and multivariable analyses while comparing the cancer and no-cancer groups. Clinical data were analysed using Chi-square and T-student analyses. A multivariable logistic regression analysis was also performed to identify any correlation between cancer detection on re-biopsy with the previously-mentioned variables, at the same time checking for potentially confusing factors.
Statistical analyses were performed with the software package SPSS version 13 (*SPSS Inc, Chicago, IL, USA*). Statistical significance was defined as a P value < 0.05.

Results

Patient's characteristics are reported in Table 1.
Plurifocal HGPIN (pHGPIN) was found in 103 pts

Table 1.
Patient characteristics and descriptive statistics.

Variable	All Patients (n = 193) no. (%)	No cancer group (n = 138) no. (%)	Cancer group (n = 55) no. (%)	P Value
Age (years)				
Mean (median)	67.3 (66)	64.7 (64)	68.7 (67)	0.001*
Range	47-83	47-79	49-83	
PSA values (ng/mL)				
Mean (median)	7.6 (8.1)	6.7 (7.0)	8.5 (8.8)	0.021*
Range	1.5-26.4	1.5-20.1	2.8-26.4	
Prostate volume (mL)				
Mean (median)	56.2 (51)	57.9 (54)	53.9 (52)	0.332*
Range	(17-160)	(23-160)	(17-95)	
DRE				
Normal	135 (69.9)	95 (68.8)	40 (72.7)	0.188§
Abnormal	58 (31.1)	43 (31.2)	15 (27.3)	
Cores taken at initial biopsy				
≤ 12	121 (62.7)	78 (56.5)	43 (78.2)	0.003§
> 12	72 (37.3)	60 (43.5)	12 (21.8)	
Cores with HGPIN				
1 (monofocal)	90 (46.6)	71 (51.4)	19 (34.5)	0.035§
≥ 2 (plurifocal)	103 (53.4)	67 (48.6)	36 (65.5)	
Time to re-biopsy (months)				
Mean (median)	10 (12)	9.5 (12)	10.7 (12)	0.252*
Range	(3-30)	(3-24)	(3-30)	

HGPIN = high grade prostatic intraepithelial neoplasia.
*T-test.
§Pearson chi-square test.

Table 2.
Univariable and multivariable logistic regression analysis in the overall population (n = 193).

	Univariable analyses		Multivariable analyses	
Variables	**OR**	**P value**	**OR**	**P value**
PSA (ng/mL) (continuous variable)	1.22	< 0.001	1.18	0.007
Prostate Volume (mL) (continuous variable)	0.954	0.009	0.966	0.01
Number of cores with HGPIN plurifocality vs monofocality	4.11	< 0.001	3.97	0.003
Number of cores at initial biopsy ≤ 12 vs > 12	3.87	< 0.001	3.62	0.012
Age (years) (continuous variable)	1.45	< 0.001	1.15	< 0.001
Variables not included in the model: DRE findings, time to re-biopsy.				

HGPIN = high grade intraepithelial neoplasia; DRE = digital rectal examination.

(53.4%) and monofocal HGPIN (mHGPIN) in 90 (46.6%). One-hundred and twenty one patients and 72 patients were submitted to ≤ 12-core and > 12-core initial biopsy, respectively.

Mean age was 67.3 ± 0.7 yrs; mean PSA 7.6 ± 4.5 ng/mL (range: 1.48 26.41 ng/mL); mean prostate volume: 56.2 ± 27.3 mL (range: 17 160).

The overall PCa detection at re-biopsy was 28.4% (55 patients). T-test analysis showed significant differences in initial PSA values (6.7 vs 8.5 ng/ml; p = 0.029), age at biopsy (64 vs 68 years; p = 0.005) between patients with benign tissue and PCa at re-biopsy. No differences was found with respect to prostate volume and time to re-biopsy. Chi square analysis showed that PCa detection was significantly higher in patients who underwent a ≤ 12-core initial PBx than in those with > 12-core (35.5% vs 16,8%; p = 0,03), and in patients with pHGPIN than in those with mHGPIN (34.9% vs 21%; p = 0,035).

No significant difference was found between pts with ≤ 12-core than in those with > 12-core initial PBx, pts with pHGPIN or mHGPIN and patients re-biopsied after or before a 12-month time span in PSA value, age, prostate volume and DRE-findings.

At multivariable logistic regression analysis, older age (p < 0.01; HR 1.15), a higher initial PSA value (p = 0.007; HR:1.18), lower prostate volume (p = 0.01; HR:0.966), pHGPIN (p = 0.003; HR:3.97) and ≤ 12-core initial biopsy (p = 0.012; HR:3.62) were independent predictors of PCa detection (Table 2).

We further analysed the 2 groups of pts submitted to ≤ 12-core (median 10 cores) and > 12-core initial PBx (median 14 cores). The pHGPIN, older age at biopsy and a time to re-biopsy greater than 12 months resulted to achieve the independent predictor status in pts with ≤ 2-core initial PBx (Table 3). On the contrary, in pts with > 12-core initial biopsy, higher PSA values and lower prostate volume were independent predictors of PCa detection (Table 4).

Table 3.
Univariable and multivariable logistic regression analysis in patients submitted to ≤ 12-core initial biopsy (n = 121).

	Univariable analyses		Multivariable analyses	
Variables	**HR**	**P value**	**HR**	**P value**
Number of cores with HGPIN plurifocality vs monofocality	4.38	< 0.001	3.91	< 0.001
Time to re-biopsy (≤ 12 months vs > 12 months)	2.18	0.013	2.26	0.026
Age (years) (continuous variable)	1.35	< 0.001	1.18	< 0.001
Variables not included in the model: PSA values, prostate volume, DRE findingy.				

HGPIN = high grade intraepithelial neoplasia; DRE = digital rectal examination.

Table 4.
Univariable and multivariable logistic regression analysis in submitted to > 12-core initial biopsy (n = 72).

	Univariable analyses		Multivariable analyses	
Variables	**OR**	**P value**	**OR**	**P value**
PSA (ng/mL) (continuous variable)	1.75	0.01	1.42	0.038
Prostate Volume (mL) (continuous variable)	0.854	0.001	0.828	0.01
Variables not included in the model: HGPIN focality, age, DRE findings, time to re-biopsy.				

HGPIN = high grade intraepithelial neoplasia; DRE = digital rectal examination.

After cancer diagnosis 35 patients underwent radical prostatectomy: organ-confined disease was found in 32 (91.4%); one patient had pT3b carcinoma at surgery and two patients were affected by pT3a carcinoma (all these patients underwent ≤ 12-core initial PBx). All patients were node negative at lymphadenectomy, with the mean Gleason score being 6.3 (two patients had Gleason score 4+3, and two had Gleason score 3+4). The remaining patients with cancer diagnosis had clinical T1c-T2a stages, mean PSA of 7,67 ng/mL and mean Gleason score of 6.1 at biopsy, thus suggesting organ-confined disease.
Of the 138 men with no cancer on repeat biopsy, 55 received a third biopsy, within a mean 14.5-month interval (range: 3-29 months) between second and third histologic examination. Seven patients had cancer detection at third biopsy (12.7%). Of those, 5 had initial diagnosis of HGPIN with ≤ 12-core initial PBx.
Eleven patients received a fourth biopsy. One patient, who received ≤ 12-core initial PBx, had cancer detection (9%).

Discussion

The clinical importance of HGPIN is due to its high predictive value as a marker for carcinoma. Considerable variations have been reported in the literature concerning its incidence (0.7 to 24%) (16-18) and risk for cancer. Many studies reported a cancer yield on re-biopsy (owing to a previous HGPIN diagnosis) ranging from 22% to 100%7,8,18-20. Particularly, the PCa detection rate after an initial HGPIN diagnosis has decreased from 40% to 50% in the early 1990s to 10% to 30% in recent studies (9-12). The change in prostate sampling from sextant to extended or double sextant protocol is considered largely responsible for this decrease (15).
Our results are within the contemporary range with a 28% PCa detection rate after an initial HGPIN diagnosis. The relatively higher percentage, when compared with the studies of *Gallo et al*. (9) and *De Nunzio et al.* (11) could be explained by the higher number of cores taken at re-biopsy (18-26 cores) and by the longer time to re-biopsy (range 3-30 months; median 12 months).
Furthermore, our data clearly demonstrate the impact of the number of cores taken at the initial biopsy in the subsequent risk of PCa detection in patients with initial diagnosis of HGPIN. PCa detection at re-biopsy was significantly higher in patients who underwent a ≤ 12-core initial PBx than in those with > 12-core (34.2% vs 16,8%; p = 0,03) and a number of cores ≤ 12 taken at the initial biopsy achieved the independent predictor status of PC detection (p = 0.012; HR:3.62).
These findings support the hypothesis that, in the era of extended biopsy protocol, HGPIN diagnosis is associated with a lower risk of PCa than in previous studies, with a detection rate that is similar to what is reported from the follow-up of initially negative biopsy (19% in our experience).
We can conclude that > 12-core initial biopsy seems to permit a sampling that is extensive enough to provide a high negative predictive value: in case of isolated HGPIN diagnosis, we can reasonably presume that the risk of missing concurrent CaP at biopsy is low and requires no aggressive repeat biopsy protocol. Patients should be monitored with yearly PSA and DRE, as proposed by *Moore et al.* (21). Indeed, in our study higher PSA value resulted as independent predictor of PCa, together with older age of the patients, in the group of patients with isolated HGPIN diagnosis obtained by > 12-core PBx.
On the contrary, in case of isolated HGPIN diagnosed by ≤ 12-core initial PBx, the PCa detection rate at subsequent biopsy is significantly higher (34%) than in patients with initially negative biopsy (19%). This result is in agreement with the guidelines of the National Comprehensive Cancer Network, that indicates extended repeat biopsy, including transition zone, if HGPIN is found in TRUS-guided PBx of less than 10 cores (23).
The need for aggressive follow-up and re-biopsy protocol, in patients with an initial isolated HGPIN diagnosis obtained with a low number of cores, is further supported by the finding that the majority of PCa detected at the third or fourth re-biopsy had ≤ 12-core initial PBx.
Another concern is whether HGPIN is associated with some parameter, that may provide better risk discrimination of PCa detection between patients with isolated HGPIN diagnosis. Several authors analysed the prognostic value of PSA, PSAD, patient age, prostate volume, abnormal DRE and/or TRUS findings in patients with initial HGPIN diagnosis. However, there is presently no consensus regarding when and how to re-biopsy patients with initial HGPIN because of the lack of a strong predictive factor suggesting a final positive biopsy.
In our study, PSA value achieve the independent predictor status only in the group of patients submitted to > 12-core initial biopsy, togheter with lower prostate volume, while older age is associate with increased risk of PCa detection in case of ≤ 12-core initial PBx.
Furthermore, we found that, pts with ≤ 12-core initial PBx, the plurifocality of HGPIN, older age at biopsy and a time to re-biopsy greater than 12 months resulted to achieve the independent predictor status of PCa detection. On the contrary, in pts with > 12-core initial biopsy, higher PSA values and lower prostate volume were independent predictors of PCa detection.
The role of HGPIN plurifocality is still controversial: in their recent paper, *Merrimen et al.* (10, 22) found that the risk of prostate cancer detection was related to the extent of HGPIN in the initial sample, with a greater likelihood of PCa when multiple prostatic sites (≥ 2 cores) were involved. Furthermore, *De Nunzio et al.* (11) suggested that a 6-months biopsy is recommended in patients with HGPIN when 4 or more cores with HGPIN are detected in the initial biopsy sample, independent of PSA values. On the contrary, according to *Gallo et al.* (9) findings, HGPIN focality did not seem to influence the subsequent diagnosis of prostate cancer.
We previously reported that, in a population of patients with initial 10-12-core biopsy, cancer detection rate in patients with mono- or pluri-focal HGPIN is statistically different (24).
Our data support the predictive role of HGPIN plurifocality, in case of initial PBx performed with 12 cores or less: patients with ≥ 2 cores with HGPIN had more than 3 times higher risk of PCa detection at re-biopsy, compared to patients with monofocal HGPIN.

On the contrary, HGPIN plurifocality was not associated with an increased risk of PCa detection when > 12 cores were taken at the initial biopsy.
Our results confirm those of *Merrimen et al.* (10, 22) and De *Nunzio et al.* (11), who found HGPIN plurifocality as a predictor of PCa in patients submitted to an initial PBx with ≤ 12 cores, as also those of *Gallo et al.* (9), who failed to demonstrate the predictive role of HGPIN plurifocality in patients submitted to initial 12 to 20-core biopsy (mean 16.3).
The re-biopsy follow-up interval is one of the main concerns in the case of initial, isolated HGPIN diagnosis. The most aggressive re-biopsy protocol reported in the literature is follow-up biopsies at 3 to 6 monthly intervals for 2 years, followed by 12 monthly intervals for life (25). *Lefkowitz et al.* (14) recently updated their study, examining the natural history of HGPIN by performing re-biopsy at a 3-year follow-up interval: 25.8% of the patients had CaP, while only 2.3% of the cases had cancer detection when performing a 1-year follow-up re-biopsy. They confirmed that HGPIN is a risk factor in the development of CaP and recommended a 3-year follow-up interval biopsy.
In our experience, in case of ≤ 12-core initial PBx, a 12-month follow-up rebiopsy seemed to provide higher detection of a pathologically organ-confined cancer, avoiding unnecessary negative biopsies (due to biopsying too soon) and reducing the risk of missing curable CaP (due to biopsying too late). In case of > 12-core initial PBx, time to re-biopsy did not affect PCa detection rate. Probably, the increased number of cores taken at initial biopsy provides a high negative predictive value and longer follow-up time to re-biopsy is needed, in order to increase PCa detection, in case the initial biopsy had missed a very low volume cancer.
Our study is not devoid of limitations. The power of our conclusion may be somewhat limited by the relative small study population and the retrospective nature of the study. The number of cores taken at initial biopsy is determined by the treating urologist and may be affected by several parameters such as PSA value, prostate volume, or DRE findings. Furthermore, our patients underwent a second set of prostate biopsies based on their personal urologist's opinion. Even if these biases may affect the results of the study no significant differences in abnormal DRE findings, prostate volume and PSA values were detected between the group of patients submitted to 12-core initial PBx or > 12-core initial biopsy and between patients re-biopsied more or less than 12 months after the first biopsy set.

Conclusions

PCa detection on saturation re-biopsy after initial diagnosis of HGPIN is significantly higher in pts submitted to ≤ 12-core than those submitted to > 12-core initial PBx. These findings support the hypothesis that, in the era of extended biopsy protocol, HGPIN diagnosis is associated with a lower risk of PCa than in previous studies, with a detection rate that is similar to what is reported from the follow-up of initially negative biopsy. More than 12-core initial biopsy seems to permit a sampling that is extensive enough to provide a high negative predictive value: in case of isolated HGPIN diagnosis, we can reasonably presume that the risk of missing concurrent CaP at biopsy is low and requires no aggressive repeat biopsy protocol.
In patients with ≤ 12-core initial biopsy pHGPIN and older age and a time to re-biopsy greater than 12 months were predictors of PCa detection at re-biopsy. In patients with > 12-core initial biopsy, higher PSA values and lower prostate volume was associated to an increased risk of PCa detection at re-biopsy.

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PRESENTATION

Biopsy of the anterior prostate gland: Technique with end-fire transrectal ultrasound.

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Summary

Objectives: *Transperineal approach is considered the best method to biopsy the anterior tissue of the prostate gland that is generally neglected by transrectal approach. We describe a technique of anterior prostate biopsy obtained with transrectal approach using an end-fire probe.*

Materials and Methods: *We correlated the images of the video of the diagnostic biopsy, the histology of the biopsy and of the surgical specimen after radical prostatectomy. A 68 years old ma previously underwent two biopsies: first biopsy and re-biopsy were performed using the transrectal approach with 12 and 16 cores respectively, including the tranisizion zone (2 per side). Initial histology revealed high grade PIN only. We performed a saturation biopsy (28 samples) under local anesthesia, as outpatient, using endfire ultrasound probe, including anterior zone and fibromuscolar stroma (2 per side). Images of the procedure was stored electronically. Each biopsy core was pre-embedded and inked at one side in order to identify the rectal end (pericapsular side). Surgical specimen of radical nervesparing prostatectomy was analyzed according to the Stanford protocol (3 mm). All biopsies and surgical specimens were reviewed by the same uro-pathologist.*

Results: *Cancer was detected only by anterior biopsy (left side, 1 core, 3 mm of total cancer extension, Gleason score 3 + 3, placed into the not inked core side). Histology of the surgical specimen confirmed the location of the disease with 0.3 cc tumor volume. Technically, to improve biopsy of the anterior zone the tip of the needle should obtain all the tissue up to the Santorini venous plexus. Postoperative recovery was uneventful after both procedures.*

Conclusion: *We showed that end-fire probe makes possible, effective and safe the biopsy of the anterior prostate, which may contain cancer in particular when previous biopsies are negative. The anterior biopsy technique herein described is easy and reliable. Based on our experience, end-fire probe should be used in re-biopsy or saturation biopsy if transrectal approach is preferred. Confirmatory randomized clinical trial should be done in the future.*

KEY WORDS: *Prostate neoplasms; Ultrasound; Saturation biopsy; Diagnosis; Radical prostatectomy; Equipment and supplies.*

INTRODUCTION

Transrectal ultrasound (TRUS) guided biopsy is the most used approach to detect prostate cancer (1). One of the weak point of the TRUS has been considered the anterior zone, since the needle tract seems not to be able to reach this area, even under ultrasound control (2, 3). The transperineal (TP) approach is believed to be the best route for anterior sampling (4).

The introduction of new endocavitary convex probe equipped with end-fire biopsy system provides two important advantages: handling and needle tract visibility (5). The first is related to the shortness of the endorectal (intracoproreal) portion, that makes all movements within the rectum easy, without patient's discomfort (6). Consequently probe handling and movements are improved due to the increase in degrees of freedom while are limited with the longer biplanar probe. The second advantage is that the entire needle track is visible under real time control and that it is in line with the major axis of the probe. This has been made possible by two techonological advances. The enlargement of the acoustic transducer form 90° to 180° and its advancement to the probe tip. The needle exit was removed from

Figure 1.
Anterior zone (grey lines) in transverse section at the mid prostate: peripheral zone (PZ), anterior horn (AH) of the peripheral zone, urethra (U), anterior fibromuscolar stroma (AFS).

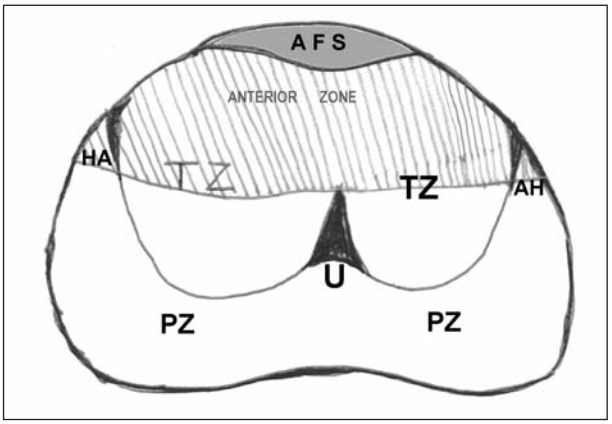


Figure 2.
Anterior zone (grey lines) in transverse section at the prostate apex.

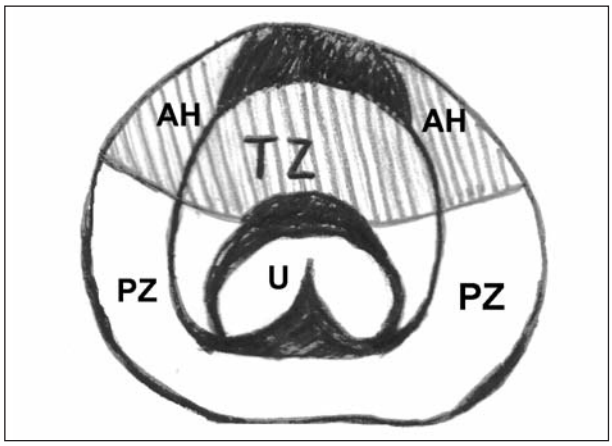
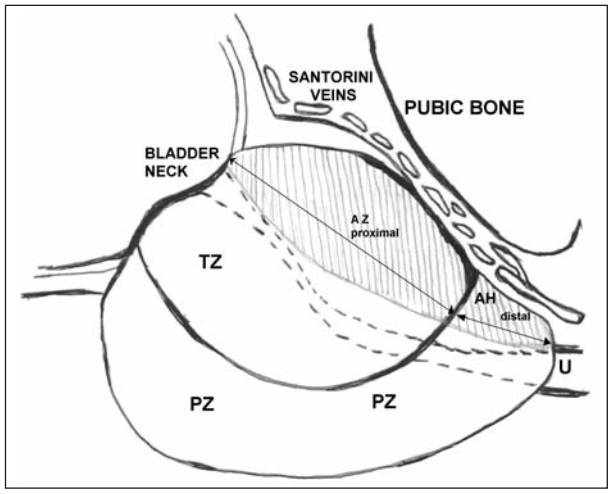


Figure 3.
Anterior zone (AZ) (grey lines) in transverse section at the mid prostate: peripheral zone (PZ), anterior horn of the peripheral zone, urethra (U).

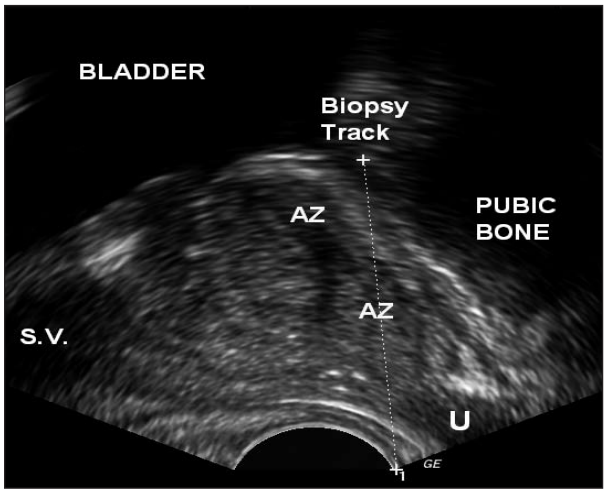


one side and was placed to the tip of the probe close to the acoustic transducer. Thus the convex endocavitary probe is called "end-fire" instead of "side-firing" probe. The convex end-fire gets the needle track always on the ultrasound monitor, making the biopsy easy and reliable on the anatomical location with the highest predictability and accuracy.
One of the main advantages of the end-fire probe seems related to biopsy of the anterior zone, but this has not been published so far (7). The anterior zone of the prostate is located on both sides of the gland, it includes parenchyma, delimited: anterior by fibromuscular stroma and anterior capsule, posterior by the plane including the prostatic urethra; cranially the bladder neck and caudally the external sphincter and pre-sphincteric urethral stump. Prostatic tissue included in the anterior area can be divided in two parts: the distal segment close to the apex, also called anterior horn (AH) of the prostatic apex and the proximal segment close to the transizion zone, including BPH tissue located anterior to the prostatic urethra up to the bladder neck (Figures 1, 2, 3, 4).
We describe a man who underwent biopsy technique of the anterior prostate with TRUS approach using end-fire probe: the images of the diagnostic biopsy have been correlated with the histology of the biopsy and surgical specimen after radical prostatectomy.

Material and Methods

We describe a 68 years old man who underwent transrectal saturation biopsy. He had 2 previous biopsies: the first 12-core biopsy was performed 2 years before and histology detected high grade PIN in 3 cores. After 10 months, he underwent at our hospital a 16-cores rebiopsy including the transizion zone using TRUS equipped with end-fire system. Hystology detected PIN in 1/16 core. He underwent saturation biopsy after 18 months from the former biopsy: prostate volume was 51 cc, serum PSA level 7.7 ng/ml, free/total PSA 17%,

Figure 4.
Biopsy track in the anetrior zone (AZ) with TRUS with end-fire, longitudinal view. (SV seminal vescicle, U Urethra)

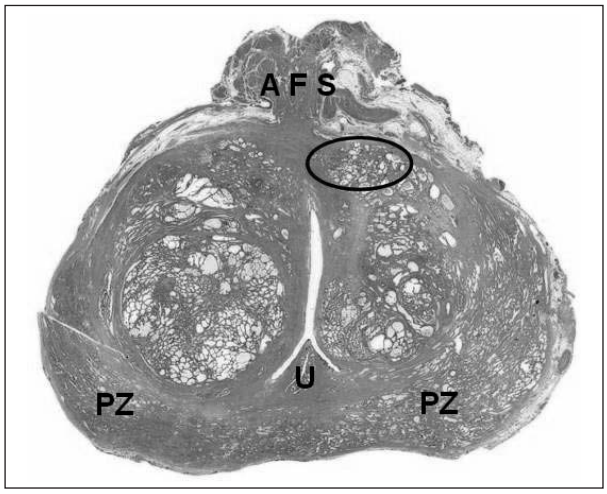


PSA Density 0.15, digital rectal examination and ultrasound were negative.
All images of the saturation biopsy were electronically stored by last generation ultrasound (Esaote) equipped with endfire convex probe (6.0-12.0 MHz, Hitachi): 28 cores were obtained using 18-gauge automatic needle (Maxicore, Bard) with 18 mm core length, under local anesthesia as outpatient procedure. Based on anatomical location: 12 biopsy were obtained in the peripheral zone (4 apex, 6 mid, 6 base) at the mid, lateral and far lateral level respectively; 6 core in the transizion zone, 4 in the anterior zone, and 2 cores in the sub-urethral median zone.
The anterior biopsy was performed pushing the needle in the prostate just close to the limit of the anterior zone using the longitudinal view. The needle firing was activate to obtain all tissue up to the Santorini venous plexus, including part of the anterior fibromuscolar stroma. Each biopsy core was pre-embedded according the sandwich technique (8) and inked at one side in order to identify the rectal end (pericapsular side). Nerve-sparing radical retropubic prostatectomy was performed after 3 months by one of the authors (ABG). The surgical specimen of radical nerve-sparing prostatectomy was analyzed according to the Standford protocol with 3 mm step sections (Figure 5). All biopsy and surgical specimens were reviewed by the same uro-pathologist. A Medline search was performed to identify key clinical studies of anterior prostate biopsy, using the search terms: prostate biopsy, prostate cancer, detection, transrectal ultrasound (TRUS), and diagnosis. Results were restricted to the English language, giving preference to those published within the last 5 years.

Results

Cancer was detected only by 1 anterior biopsy of the prostate using a 28-core saturation biopsy. Biopsy cancer was located in the left side in 1 of 4 AZ cores, 3 mm of total cancer extension, Gleason score was 3 + 3, clinical stage was T1c. Tumor was found located at one end of the biopsy fragment, in the not inked side. Histology of the surgical specimen confirmed the exact location of the disease (Figure 5). Two cancer foci were discovered: the main focus (index lesion, 0.3 cc of volume) was located in the anterior left side, 1.6 cm in the main diameter, the second small focus was in the right peripheral zone (0.03 cc). Pathological staging was pT2c pR0 pLVI0 pN0 (7 lymph nodes) according to 2009 TNM and ISUP 2005 Gleason grading revision. Postoperative recovery was regular after biopsy and prostatectomy.

Figure 5.
Transverse section of the whole prostate on histology section after nerve-sparing surgery.
The black circle show the cancer location.
Anterior fibromuscolar stroma (AFS).



Discussion

Echo-guided guided systemic biopsy with a minimum of 10 systemic cores at initial biopsy of the peripheral zone is recommended. Repeated biopsies should be more extended (> 10 cores) and directed more laterally in the peripheral and transition zone. One set of repeat biopsies is warranted in cases with persistent suspicion including the transition zone. Saturation biopsy (≥ 20 cores) should be reserved for repeat biopsy only in selected cases (9). Aim of saturation biopsy is cancer detection in previously unsampled areas. Prostate anterior zone is generally neglected by standard biopsies and even transition biopsy may miss this area (10-12). Based on pathological analysis, cancer arises more frequently in the far anterior subcapsular tissue that lies below the Santorini venous plexus (13).
The TP approach was so far believed to be the best way of sampling the anterior prostate. Authors recently proposed to combine TRUS and TP biopsy (14), but this technique has disadvantages and relevant costs.
There are 2 types of transrectal ultrasound probe, that is side-fire and end-fire. Although each configuration provides adequate imaging of the gland, the main difference in the biopsy configuration is that a side fire probe is limited to a biopsy trajectory in a longitudinal axis (apex-to-base) (15). Biopsy of the anterior zone is difficult to perform using side-fire probe, since it has longitudinal transducers, allowing imaging and biopsy in the longitudinal and transverse views. The transverse arrangement requires that the probe be placed posterior to the gland, so that the needle exits the probe in a fixed angulation, few centimeters proximally to the acoustic window. This makes biopsy of the anterior gland difficult and possible only through significant torque of the probe (16, 17). Furthermore needle tip will cause pain in the anterior biopsy since the needle transverses the rectum above the dentate line (18).
The end-fire probe enables biopsy cores to be taken more transversely (oriented in an anterior-posterior axis) and has a more oblique angled trajectory, allowing direct anterior sampling. End fire probes has more flexibility in maneuvering the biopsy direction than side fire probe and the needle can pass more directly into the prostate toward its anterior aspect.
Ching et al. showed that end-fire probes provide a statistically significant improvement in the PCa detection rate compared with side-fire probes (45.8% vs 38.5% respectively) (6). *Paul at al.* found similar differences in detection

rate 25.3% vs a 15.0% respectively in patient with negative DRE and PSA between 4 and 10 ng/ml (19). The authors believe that the reason could be the facilitated sampling in the most lateral part of the peripheral zone and apex. Despite the widespread use of end-fire technology, the literature published on this field is very limited. For the first time, we report that end-fire probe increases the detection rate due to facilitated sampling of the far anterior zone and not only the most lateral peripheral zone.

Advantages of the end-fire technique area: real time identification and control of the all needle tract, including angulation, short learning curve, reproducible, rapid, and effective.

The proximal segment of the AZ is usually missed by transrectal transition biopsy. Technically in order to make sure to completely sample all the AZ during biopsy the tip of the needle should obtain all tissue up to the Santorini venous plexus, including the medial fibromuscular stroma. The distal segment of the AZ is composed from apical tissue, called anterior horn, and should be sampled at the first biopsy.

In our case, a small volume prostate cancer was detected. This can be considered not clinically relevant (20). On the other hand these lesions may be potentially invasive due to the risk of early extension in extraprostatic tissue (21).

Our technique is not influenced by prostatic volume (unpublished data). Anyway the TP is influenced by prostatic volume and body habitus due to pubic arch interference to the needle insertion from perineal access. In case of bening prostatic enlargment (> 50 cc) the far anterior prostate is displaced toward pubic bone. The TRUS is not influenced by pubic arch in any case due to different acoustic window.

Overall recommendations for anterior biopsies area the following:

1. Indicated in saturation or re-biopsy setting;
2. PIN or Atypical Small Acinar Proliferation located in the transition zone;
3. Elevated PSA with negative DRE;
4. Hypoechoic area in the anterior stroma (22);
5. Large prostate (> 50 cc);
6. Indication to saturation biopsy has to be made based on an individual patient.

Based on our experience, contraindications to transrectal approach are: disease of the rectal wall, anal diseases or anal stricture, hearth valves disease, high risk of infection (immunodepression) and relevant bladder outlet obstruction. In those patients TP approach is recommended.

There are several limits in our study. Complications and diagnostic accuracy should be evaluated on large numbers. Verification bias limits the analysis of anterior prostate biopsy study results, however this study can be considered scientific evidence as case report and expert opinion. Further studies should be done to improve the level of evidence.

Conclusions

The anterior zone is generally neglected by extended biopsies using transrectal approach. We show that end-fire probe facilitates the sampling of the far anterior zone, which may contain cancer in particular when previous biopsies are negative. The anterior biopsy technique is effective, safe, easy and reliable. Based on our experience, end-fire probe should be used in all re-biopsy or saturation biopsy rather than side-fire transrectal probe. Confirmatory randomized clinical trial should be done in the future.

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PRESENTATION

High-intensity focused ultrasound (HIFU) in prostate cancer: A single centre experience in patients with low, intermediate or high-risk of progression.

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Summary

Objective: *High-intensity focused ultrasound (HIFU) is a minimally invasive treatment based on thermal ablation of tissues which are warmed up to 85°C in the focal area. Clinical studies have shown such treatment modality to be safe and effective in the management of localised prostate cancer as well as of local recurrences after radical prostatectomy or radiotherapy.*

Material and Methods: *From May 2002 to June 2010, 171 patients with no previous treatment for prostate cancer, aged 44 to 86 years (mean 74.7) underwent 197 HIFU treatments; 22 patients needed a second treatment as the first was incomplete (4 patients) or because of recurrence (18 patients). The prognosis subgroups were defined as low-risk in 29 patients (clinical stage T1-T2a, PSA < or = 10 ng/mL and Gleason score lower than 7), intermediate-risk in 47 patients (clinical stage T2b or PSA 10 - 20 ng/mL or Gleason score of 7), and high-risk in 95 patients (clinical stage > or = T2c or PSA > 20 ng/mL or Gleason score higher than 7).*

Results: *At a mean follow-up of 67.9 months, biochemical success rate (PSA constantly < 0.5 ng/ml) was obtained in 84.2% of low and intermediate risk patients and in 43.1% of high risk patients; post-treatment biopsies (6 months after treatment) revealed no residual tumour in 93.4% of low or intermediate risk patients and in 63.1% of high risk patients.*

Conclusions: *Radical prostatectomy remains the "gold standard" for localised prostate cancer. However, HIFU seems to be a promising alternative and less invasive treatment modality with an encouraging success rate, at least in the short-term, in patients with low and medium risk of progression, not candidates for radical surgery; in cancers with clinical stage > or = T2c, or PSA > 20 ng/mL, or Gleason score higher than 7 seems to get good results in about half of patients.*

KEY WORDS: *High-intensity focused ultrasound (HIFU), Prostate cancer.*

INTRODUCTION

High-intensity focused ultrasound technology (HIFU) is a minimally invasive treatment based on thermal ablation of tissues which are warmed up to 85°C in the focal area. Initial studies have shown that HIFU administered via a transrectal probe is capable of creating prostate lesions without injury to intervening and surrounding tissue.

The growing interest in HIFU is mainly due to its many potential applications as a new energy source and as noninvasive therapy. It has been introduced to urological oncology as a transrectal treatment for prostate cancer and as extracorporeal treatment for kidney cancer. Although its application in the kidney is still at the clinical feasibility phase, HIFU technology is currently being used in daily practice in Europe for the treatment of prostate cancer (1).

Clinical studies have shown such treatment modality to be safe and effective in the management of localised prostate cancer (2, 3) as well as of local recurrences after radical prostatectomy or radiotherapy (4, 5), but there are still few data in patients with high-risk localised prostate cancer: > o = T2c or Gleason score 8-10 or PSA > 20 (6).

HIFU is currently used as primary treatment for patients with localized prostate cancer T1-2 N0-X M0, mostly low and intermediate risk, not suitable for surgery and as salvage treatment for locally proven recurrence of prostate cancer after curative therapy.

Material and methods

From May 2002 to June 2010, 171 consecutive patients with prostate cancer, aged 44 to 86 years (mean 74.7) underwent 197 HIFU treatments; 22 patients needed a second treatment as the first was incomplete (4 patients) or because of recurrence (18 patients). The patients received a mean of 1.15 HIFU sessions.

Indications for HIFU treatment included patient's choice or not eligible to radical prostatectomy because age (> 75 years) or high anaesthesiological risk or PSA > 20 ng/ml or clinical stage > or = T3.

The mean prostate volume was 38.5 ml (range 9-172 ml), the mean serum PSA concentration was 27.9 ng/ml (range 0,1-143) and mean Gleason sum 6.3 (range 3-9).

The prognosis subgroups were defined as low-risk in 29 patients (clinical stage T1-T2a, PSA < or = 10 ng/mL and Gleason score lower than 7), intermediate-risk in 47 patients (clinical stage T2b or PSA 10 - 20 ng/mL or Gleason score of 7), and high-risk in 95 patients (clinical stage > or = T2c or PSA > 20 ng/mL or Gleason score higher than 7) with localized (70 pts) or locally advanced prostate cancer (24 patients T3 and 1 patient T4).

Preoperative assessment included renal, bladder and transrectal prostatic ultrasounds, uroflowmetry, as well as I-PSS, QoL and IIEF-5 questionnaires.

CT scan and bone scan were performed only in patients with PSA > 10ng/ml.

All patients received spinal anaesthesia. After placing a suprapubic catheter, and performing a debulking TUR of the transition zone of the prostate to prevent postoperative retention due to sloughing and necrosis, HIFU treatment was carried out with a transrectal probe (*ABLATHERM*, *EDAP TECHNOMED*).

Results

Follow-up included PSA determination after 6 and 12 weeks and then every 3 months, transrectal prostatic biopsy after 6 months, I-PSS, and QoL and IIEF-5 questionnaires every 3 months.

At a mean follow-up of 67.9 months, biochemical success rate (PSA constantly < 0.5 ng/ml) was obtained in 84.2% of low and intermediate risk patients and in 43.1% of high risk patients; post-treatment biopsies (6 months after treatment) revealed no residual tumour in 93.4% of low or intermediate risk patients and in 63.1% of high risk patients.

No severe side-effects (except 1 rectourethral fistula 0.6%) were observed in this population: asymptomatic urinary tract infections (17.5%), haematuria (3.5%), prostatitis (2.9%), epididymorchitis (1.8%), emorrhoidal pain (0.6%), strictures of urethra (7.6%) and bladder neck sclerosis (12.2%). Light stress incontinence occurred in 4.0% of the patients and erectile dysfunction in 77.7%. These outcomes certainly temper the enthusiasm for HIFU as a minimally invasive treatment alternative.

Discussion

Radical prostatectomy remains the "gold standard" for localised prostate cancer.

However, HIFU seems to be a promising alternative and less invasive treatment modality with an encouraging success rate, at least in the short-term, in patients with low and medium risk of progression, not candidates for radical surgery; in our series, in cancers with clinical stage > or = T2c, or PSA > 20 ng/mL, or Gleason score higher than 7 seems to get good results in about half of patients.

HIFU appears to be a valid alternative to active surveillance protocols in low-risk patients and standard therapies in patients with life expectancies of 10 or fewer years (7). It is a repeatable technique and multisession treatments or salvage treatment can be applied safely.

The treatment of prostate cancer using HIFU is accepted well by the patient, quality of life is preserved, but there is significant degradation of the sexual function and more moderately of the urinary function (8). A longer interval between TURP and HIFU (> 1 month) might reduce the risk for the development of BOO. By modifying the treatment protocol, it is possible to improve the rate of postoperative potency up to 40-60%, using a nerve-sparing protocol. However the increase of sparing procedures will increase the percentage of local failure.

No randomized controlled trials or meta-analyses comparing HIFU with currently accepted management approaches were identified.

Long-term success rate (9) and outcome of complications, particularly strictures (10, 11), remain to be defined to determine to exact role of this treatment option in managing prostate cancer.

Conclusions

HIFU is currently not recommended as an alternative to accepted curative treatment approaches for localized prostate cancer (12). Considering the available short-term results, the last version of the *European Association of Urology Guidelines* still considered HIFU as an investigational treatment, a longer follow-up being needed to assess its true role in the management of prostate cancer

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PRESENTATION

The role of endorectal ultrasonography in preoperative staging of rectal cancer.

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Summary

Objectives: *The aim of this paper is to enlight the role of endorectal ultrasonography in the preoperative staging of rectal cancer.*
Methods: *83 patients having rectal cancer and candidates to surgery were studied with endorectal ultrasonography with a probe at a frequency up to 7.5 MHz probe. Eighteen patients were diagnosed with a cancer at A stage, 38 with a neoplasia at B stage and 37 at C stage.*
Results: *In all patients the examination revealed an involvement of the rectal muscular tunica. Sixtyseven patients presented mesorectal invasion, 17 patients showed the involvement of adjoining structures, and 27 patients presented pathological lymph nodes.*
Conclusions: *Endorectal ultrasonography allows to distinguish patients having rectal cancer limited to the mucosa or invading sub-mucosa regions from those having a more indepth invasion. Apart from this, endorectal ultrasonography is not able of discriminate reactive lymph nodes from metastatic ones.*

KEY WORDS: *Endorectal ultrasonography; Rectal cancer.*

INTRODUCTION

It is almost a decade that the endorectal ultrasonography (ERUS) has been recognized as a routinary exam for the study of prostatic pathologies. The discovery of echographic 360° transversal scan probes and of the most recent three-dimensional (3D) probes has permitted in-depth studies of both the rectal wall anatomy and the entire structure of the small pelvis. For this reason in the last few years, general surgeons, with the collaboration of urologist colleagues, have decided to treat all those patients having rectal cancer and needing pre-operative local-regional staging with an endorectal ultrasonography exam (4, 5). This type of exam, carried out by experts of the sector, supplies with important information about the depth of the invasion, the involvement of mesorectal lymph nodes and the involvement of perirectal structures. These important news let the surgeon select the patients who should be immediately operated (anterior resection, transanal endoscopic microsurgery (TEM)) (6). Those presenting an advanced local disease should instead be redirected towards the radiotherapist or to the cancer specialists in order to receive a preoperative chemoradiotherapy (1). Moreover, during the follow-up stage, ERUS has proved to be a valid tool for following the patient either after the cancer resection or after the chemoradiotherapy.

METHODS

During the period starting from January 2005 and ending in February 2010, we have treated 83 patients showing rectal cancer and candidates to surgery, with an endorectal ultrasonography exam through the use of a multiplanes probe functioning at a variable frequency up to 7.5 MHz. The diagnosis of the rectal cancer was established through the use of colonscopy, histological exam (biopsy), abdominal-pelvic CAT scan and, in the last years, magnetic resonance imaging (MRI). To correctly carry out the endorectal ultrasonography exam, a low enema was given to all the patients and the probe was covered with a condom to avoid any contamination. In 22 patients the cancer was localized in the lowest part of the rectal wall; in 40 patients it was placed in the median part of the rectum. In the remaining 21 patients the cancer was situated in the upper part of the rectum.

Lastly, 18 patients were diagnosed with a cancer at A stage, 38 with a neoplasia at B stage and 37 at C stage.

Results

Endorectal ultrasonography in all patients has revealed the involvement of the rectal muscular tunica. In 67 patients (80%) we found mesorectal invasion, confirmed by the histological exam; in 16 patients (19%) this invasion was absent. The involvement of adjoining structures was assessed in 17 patients (20%). Lastly, in 27 patients (32%) the endorectal ultrasonography exam has highlighted the presence of pathological lymph nodes (we currently don't know if these nodes are reactive or metastatic).

Discussion

In the last eighty years three methods have been used for the staging of rectal cancer: Dukes' classification (three categories: A - cancer confined to the rectal wall without metastatic lymph nodes, B - cancer extended to the perirectal tissue without metastatic lymph node, C - metastatic lymph nodes), categorization by *Hastler et al.* and TNM. From that point on, it has been recognized the need for a more reliable system for the pre-operative staging of the rectal cancer (1). This system should be aimed at acquiring more precise information, whether about rectal wall or about pelvic organs adjoined to it. The final aim of all these methods is to find a correct treatment for this kind of pathology. Therefore, in the last twenty years the new technique of endorectal ultrasonography with the use of 360° transversal scan probes and of the most recent three-dimensional (3D) probes has become an efficient tool for the diagnosis and treatment of rectal cancer (1, 5).

If carried out by experts, this exam permits studying a rectal section of 14 cm. in length starting from anulus anale; the rectal wall is constituted by five layers: the first, the third and the fifth layer are hyperechoic, while the second and the fourth are hypoechoic. To be more precise, the first and the third layers represent echoic reflection phenomena; the second layer is constituted by mucosa and sub mucosa. The fourth and fifth layers are referred to the muscular and adipose layers, respectively (2).

Several studies have reported the diagnostic precision of ERUS in the evaluation of the rectal cancer, assessing it between 81% and 94%, as far as the cancer invasion depth and the mesorectal lymph nodes involvement are concerned (1). Thanks to this assessment, operators can discern lesions which may be treated with a local excision, referred as TEM (6, 7), from those which have to be treated with more extended operations, like the anterior resection or the abdominalperineal resection (Miles).

Moreover, this parameter allows the selection of patients who have to be candidates for a chemoradiotherapy adjuvant therapy (T3-T4 and cancers which infiltrate sphincters). ERUS allows also the evaluation of lesions dimension and the parietal wall. Recently, tridimensional imaging in transrectal exams has permitted a better knowledge of the various anatomic structures and tumors. The size, location and local extent of the lesion can be found thanks to the use of additional scan planes (1, 8).

Moreover, this kind of exam can provide useful information for a precise surgery planning. As regards the assessment of the perirectal lymph nodes infiltration, ERUS show a low level of accuracy, with a sensitivity of 50-57%: the exam allows only the detection of lymph nodes which are very close to the rectal wall, impeding the distinction of inflammatory lymph nodes from the metastatic ones (3). Moreover, this methodology presents other kinds of limits when the tumoral lesions are stenotic or are voluminous and vegetating. Indeed, these features impede or make difficult the insertion of the probe.

Another limit of ERUS is represented by the interpretation errors. Two kinds of errors can happen: over-staging and under-staging. Over-staging errors can be caused by the presence of peritumoral inflammatory reaction, by pre-operative radiotherapy or by hemorrhages of rectal wall immediately after a biopsy. As far as understaging is concerned, this event, despite being less common, can have serious consequences for the patient. Indeed, when understaging occurs, a tumor can be treated inadequately, leading to a second procedure. As highlighted by the literature, understaging occurs in case of stenotic lesions; in these cases the tumor may not have been examined. Moreover, understaging can occur in tumors which are minimally invasive.

Indeed, in a case in which lymph nodes involvement is not put forward by ultrasound, a tumor can be understaged. This can lead to a local excision and to disastrous consequences of retained tumor, reduced survival and early recurrence (3).

Conclusions

At the present state ERUS allows the recognition, with a high degree of accuracy, of rectal cancer limited to the mucosa or invading sub-mucosa regions.

Moreover, ERUS is able of discerning these types of pathologies from cancer invading more in depth the patient (mesorectal or perirectal fat infiltration). This kind of diagnostic piece of data is fundamental for a more precise preoperative staging, giving more detailed information to the surgeons in order to create a better operations planning (local excision, anterior resection operation, anterior laparoscopic resection or abdominalperineal resection according to Miles' technique). In addition to this, ERUS is also a good exam technique for the indication of a chemoradiotherapic adjuvant preoperative treatment.

As regards the assessment of lymph nodes infiltration, ERUS is only able of locating lymph nodes which are located very close to the rectal wall. A clear cut between reactive and metastatic lymph nodes cannot be obtained.

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PRESENTATION

Endorectal ultrasound and magnetic resonance imaging (MRI) scan in rectal cancer: A comparative study.

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Summary

Objectives: *Endorectal ultrasound was compared with magnetic resonance imaging (MRI) in the preoperative staging for patients with Rectal Cancer. Diagnostic accuracy was assessed with regards to the factors that might influence the risk of local relapse such as T, N and CRM (circumferential resection margin).*

Methods: *From January 2006 to April 2010, 64 patients with rectal cancer were studied preoperatively either by means of MRI scan of the pelvis or endorectal ultrasound scan in order to assess the intramural extension. For 30 out of 64 patients both methods were used (comparing instrumental with histopathological data) while for 34 patiens over 64 only ultrasound scan was used.*

Results: *Endorectal ultrasound resulted to be more reliable in defining the T (parietal infiltration of the tumor) whereas MRI better defined CRM.*

Conclusions: *Both methods are reliable and complementary enabling an accurate staging of patients with rectal cancer.*

KEY WORDS: *Endorectal ultrasound; Magnetic resonance imaging (MRI); Rectal cancer.*

INTRODUCTION

Publications in the recent years report that prognosis for patients with rectal cancer, who have been operated, is directly related either to the extension of the tumoral invasion through the bowel walls and the mesorectal fat or to the propriety of circumferential resection margin (CRM). Therefore, it is important to refine imaging techniques for improving at best preoperative staging. In this way it is possible to select patients who mainly risk local relapse and who can benefit from neoadjuvant radio-chemotherapy.

For this scope, endorectal ultrasound and MRI scan are instrumental tests that have been refined over the last decade, resulting in a remarkable help for the staging and treatment of these patients.

METHODS

From January 1st to April 30th 2010, 64 patients with rectal cancer have been studied in a preoperative stage either by means of MRI scan of the pelvis or endorectal ultrasound in order to assess the intramural and extramural extension: 30/64 with both techniques, while 34/64 only with ultrasound test.

RESULTS

For the 30 patients studied with both techniques (20 patients with a T3 cancer, 7 patients with a T2 cancer, 3 patients with a T1 cancer), the instrumental datum has been compared with histopathological one: for 18/30 the T stage, obtained by means of ultrasound, coincided with histology, while only for 7/18 patients such concordance also occurred for MRI. For the remaining 12/30 cases, the preoperative instrumental datum would not coincide with both of the two techniques and also with the histology due to a misleading overstaging either from the ultrasound or from the MRI or both.

However MRI, compared to histological test, was accurate enough to detect the depth of cancer invasion through the mesorectum in 13/30 cases.

34/64 cases which were studied only by means of endorectal ultrasound all corresponded to tumour advanced stages (24 were T3 and 10 T4).

DISCUSSION

In a publication on *Radiology* (3), *Beets-Tan* and *Beets* summarised the preoperative instrumental staging ques-

tion, for patients with rectal cancer, by observing that the challenge for imaging techniques is to select subgroups of patients with different risk of local relapse. The group of patients with a superficial cancer can be treated only with surgery. The group of patients with a resectable cancer and large circumferential resection margins (CRM) can be treated with a short radiotherapy cycle followed by TME. The group of patients with advanced stage cancer or with close or infiltrated resection margins require a longer cycle of neoadjuvant chemo-radiotherapy and a more extensive surgery.

In order to win this challenge, magnetic resonance (MR) and endorectal ulrasound scan both improved largely their diagnostic accuracy. Alternatively, attempts to demonstrate the primacy of one over the other have been made. Indeed, the two techniques have resulted in being complementary and they can give accurate information on different but equally important parameters.

Therefore, the various studies have established some crucial points (or at least to be considered so) until technology will further develop:

1. T is certainly better defined by endorectal ultrasound scan. If this test is carried out by experienced personnel it can reach a diagnostic accuracy which spans between 64 and 95% , with regards to the neoplasia invasion through the various layers of the rectal wall (2);
2. MRI scan is more accurate in detecting the stage of neoplasia penetration into the mesorectal fat (mesorectum) (1, 3, 9]. Thus, the MRI scan allows to "measure" what will be the CRM (circumferential resection margins) with an accuracy that spans between 93 and 97%; as a result we can distinguish two T3 tumour subgroups, one with large CRM and one with close or infiltrated CRM.

However, it is important to remember that ultrasonography is still a less expensive and faster test than the MR and can better give tridimensional measures of the tumour (2, 5).

Nevertheless, endorectal ultrasound and MR have got limits (2-4, 6).

Ultrasound limits mainly occur with extensive sessile lesions, or generally with large vegetant lesion, because the balloon does not completely adapt to the lesion and thus, it does not achieve an optimal acoustic contact. When there is not a good acoustic contact, the air creates altered images and therefore it is difficult to detect a potential lesion invasion into the sub mucous membrane. T3 stenosing lesions can also impede or make it difficult for the ultrasound probe to pass, thus not giving the possibility to carry out a reliable test.

Ultrasound overstaging is more frequent than understaging. Tumor can be overstaged because of the presence of edema, peritumoral phlogosis, previous biopsies, balloon overdistension (that squeezes the lesion and parietal layers not permitting an accurate differentiation). In particular an overstaging from T1 to T2 can be determined by the fact that the peritumoural phlogosis is hypoechogenic as well as the tumoural tissue itself.

An ultrasound understaging occurs when it is not possible to detect invasive microfoci.

With regards to the MRI scan, the main interpretation difficulties occur when the tumor shows "spiculations" that almost reach mesorectal fascia. This happens not only in irradiated patients but also in non-irradiated cancers, especially for tumours that show a large desmoplastic reaction. It is difficult to diagnose whether such "spiculations" are due to desmoplastic reaction or neoplastic tokens.

A lower anterior location of the tumour limits the possibility to estimate the distance from the mesorectal fascia by means of MRI scan (2, 3, 7). The distal mesorectum contains little mesorectal fat and thus, when the tumour crosses the rectal wall anteriorly, it comes close to or invades the mesorectal fascia inevitably. This mainly occurs in large and lower tumours because the fat between the tumor and adjacent structures can be hidden by the neoplasia volume. In these particular cases it could be difficult to distinguish between adjacent organ compression (vaginal wall, seminal vescicles, prostate) and tumoural invasion of the organs.

Endorectal ultrasonography, for patients treated with neoadjuvant chemo-radiotherapy or in the follow-up of operated patients, deserves a separate discussion.

In both those cases ultrasonography encounters major difficulties.

For instance, after irradiation the rectal wall is thickened and more hypoechogenic and it is difficult to visualise the different layers. Therefore, overstaging is very common for these patients.

With regards to the operated patient follow-up, ultrasonography is ideal for diagnosing anastomotic relapse, provided that the probe is able to reach anastomosis.

Also in these cases tough, cicatricial tissue must be distinguished by remaining or relapsed tumour tissue. In these particular cases, operator dependance in rectal ultrasonography diagnose is mainly visible. Undoubtedly, MRI is a less operator dependent and a more reliable test.

In local relapse diagnosis, MRI is considered to be better than CAT scan for tissue characterization because it has an accuracy that spans from 75 to 93% and a sensitivity of 91-100%.

Ultrasonography accuracy in these cases could be not more than 79% (2).

N diagnosis is less simple and accurate than T for both techniques (5, 7).

Conclusion

MRI and endorectal ultrasonography are still complementary techniques and very useful in rectal cancer patient staging. Their use is mainly influenced not only by the availability of such instruments and methods in the various diagnosis and cure centres, but also by the specific operator experience (8).

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PRESENTATION

Correlation between testicular parenchymal echogenicity and male infertility.

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Summary

Objective: To verify the correlation between echogenicity of testicular parenchyma and male fertility parameters.
Materials and Methods: The study included 101 patients who referred to the urologists for couple infertility. Male patient underwent anamnestic assessment, physical examination, screening for hormonal serum levels (FSH, LH, testosterone, prolactine), sperm analysis, sperm culture and testicular ultrasound with registration of testicular volume and mean testicular echogenicity. The data has been recorded in a database and analyzed for possible statistical correlations.
Results: The variable "mean testicular echogenicity" was compared with every response variable. Non-statistical significance was found between mean testicular echogenicity and mean serum levels of testosterone, prolactin, and patient age or with the single semen sample parameters.
Conclusions: Mean testicular echogenicity does not correlate with any of the male fertility parameters examined. Higher numbers are needed to define the possible role of parenchymal echogenicity to predict infertile patients.

KEY WORDS: *Testicular ultrasound; Testicular echogenicity; Male infertility.*

INTRODUCTION

The tendency to delay the formation of a family in industrialized countries has caused an ongoing inability to conception of "older" couples. Today 15 to 30% of couples are unable to conceive after 12 months of contraceptive-free intercourse. This is also the definition of infertility by the *WHO* and *EAU guidelines* (1-2).
Within a couple, different factors, which may lead to a decrease in the fertility of one or both of the partners, may be present. These factors, which can show a spontaneous regression in a varying number of cases, define what is commonly addressed as condition of "subfertility".
Furthermore, the presence of a physiological, but reduced fertility, can lead to inability to conceive, when simultaneously present in both of the couples' members. This seems to be the case in another 30% of couples.
There are various causes for male infertility (3):
– Inherited or acquired urogenital anomalies (16.4%)
– UTI's (8%)
– Intrascrotal temperature increase (15.6%)
– Endocrine disorders (8.9%)
– Genetic anomalies
– Immunological factors (4.5%)
– Idiopathic forms (30-40%)

To obtain an accurate diagnosis, and to have the tools for a correct management of infertility, the *EAU guidelines* recommend the simultaneous examination of both partners, as female infertility may influence the couple's ability to conceive as a whole (4).
Urologists and Andrologists should look for anomalies of the genitourinary tract in every male with fertility problems. In addition, screening campaigns could lead to an early detection of people with low semen quality and could possibly improve the chances of restoring normal fertility. Both of these aspects are increasingly being investigated via ultrasonography, on account of the steadily increasing availability of color Doppler capable, high definition probes, in addition to its' relatively low costs and its' non-invasiveness, even if a thorough US study of the testis and epididymis requires a good amount of operator experience. Object of our study is to verify if there is a correlation between echogenicity of testicular parenchyma and fertility status (5).

Materials and methods

101 patients who referred to the urologists for couple infertility composed the population of our study. Beside the study of the female partner, every male patient underwent a first line anamnestic assessment including: age, general medical history, occupation, duration of unfruitful attempts to conceive, frequency of intercourse, along with the investigation for factors such as endocrine disorders, assumption of medical drugs, use of narcotic drugs, alcohol and tobacco use, exposition to toxic agents, prior UTI's, systemic diseases or prior pelvic surgery.

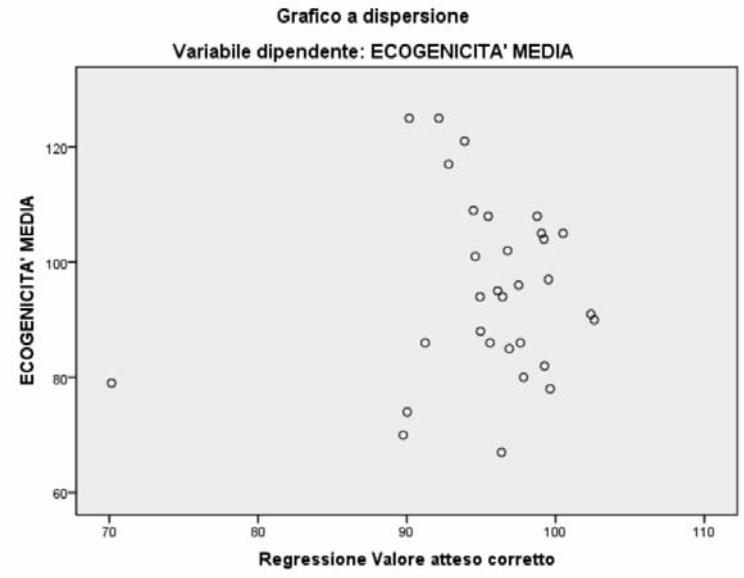
On physical examination we evaluated the expression of secondary sexual traits, the presence of varicocele, of palpable masses of the testis, of the epididymis, or of gonadal asymmetry (6).

Patients were also screened for serum FSH, LH, testosterone and prolactine levels and underwent a sperm analysis and culture (sampled after 3 days of abstinence and examined within 2 hrs). Sperm analysis included sperm volume and fluidification, concentration, motility, quantity of typical and atypical sperm morphology and presence of polymorphonuclear leukocytes.

All patients underwent testicular ultrasonography (*Voluson E8 - General Electrics®*) with a linear 13 MHz probe at the *International Associated Research Institute for Human Reproduction (Rome, Italy)*. Testicular volume (ellipsoid formula: 0,52 multiplied by the three testicular diameters) was registered and an area of 3 cm^2 (1,5 cm x 1,5 cm) was highlighted and used to assess the mean echogenicity. The ultrasonographically highlighted area was analyzed via specific software (*Voluson E8 - General Electrics®*), with which we obtained a numeric value which corresponds to mean parenchymal echogenicity; relative standard deviation of the obtained values was also calculated. Testicular tumors, cysts, or presence of varicocele were also looked for.

The data from lab results, sperm analysis parameters and US findings has been recorded in a database and analyzed for possible statistical correlations.

Figure 1.



Mean testicular echogenicity represented our dependent variable and it was associated with the other recorded data parameters (response variables). Response variables were eight: patient age, testicular volume, serum FSH, LH, prolactin, testosterone, volume of semen sample and percentage of sperm motility.

Results

All mean numeric values of our populations' response variables were calculated and gave the following results:

- Mean age: 38,8 years (range 25-61);
- Mean FSH: 9,82 mUI/mL (range 1.7-40.8);
- Mean LH: 5,00 mUI/mL (range 0,85-17,5);
- Mean prolactin: 29,21 ng/mL (range 4,8-211);
- Mean testosterone: 5,13 ng/mL (range 0,7-25,2);
- Mean testicular volume at US: 17,18 ml for the right testicle (range 2,41-37,73) and 17,03 ml for the left testicle (range 1,19-35,81);
- Mean semen sample volume: 2,06 ml (range 4,00-0,3);
- Mean percentage of sperm motility: 46,98% (range 0-80);
- Mean testicular echogenicity: right testicle 86,65 (range 136-72), left testicle: 86,59 (range 125-74).
- Mean sperm count: 44.03 x 10^6/ml (range 0-231.6 x 10^6/ml)

Other variables, such as sperm fluidity and leucocyte count were not considered in the analysis since they did not show significant inter-patient variations. Atypical sperm morphology was less than 30% in all patients.

The variable "mean testicular echogenicity" was compared with every response variable.

Non-statistical significance was found between mean testicular echogenicity and mean serum levels of testosterone, prolactin, and patient age or with the single semen sample parameters.

A certain grade of negative correlation was found between mean testicular echogenicity and mean FSH, LH levels and testicular volumes, but also in this case statistical significance ($p < 0,01$) was not reached. This is confirmed by the dispersion diagram that was constructed with the collected data (Figure 1). Correlation of the dependant variable "mean testicular echogenicity" was 0,11 with testis volume, -0,32 with FSH, and -0,24 with LH respectively.

Discussion

Mean testicular echogenicity does not correlate with any of the male fertility parameters examined, but higher numbers are needed to define it's possible role to predict infertile patients.

Anyhow, research for possible correlations between ultrasonographic findings and the examined variables should not aspire to substitute the currently available invasive methods for the diag-

nosis of infertility, but should rather aim to becoming a possibly useful tool in the evaluation of infertile patients.

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PRESENTATION

A prospective study on patient's erectile function following transrectal ultrasound guided prostate biopsy.

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Summary

Objectives: *This study is intended to assess variation of sexual function in 222 patient at different treatment stages of prostate cancer with the aid of a validated questionnaire in comparison with patients diagnosed with a benign lesion.*
The questionnaire covers the period before carrying out prostate biopsy, the disclosure of histological examination, and the recovery period.
Material and Methods: *240 patients who were to undergo trans-rectal ultrasound guided prostate biopsy due to suspected prostate cancer were consecutively and prospectively studied between January 2008 and January 2009. Patients were asked to complete an IIEF-15 questionnaire to assess sexual function during the initial consultation (T0), generally whilst they waited to be called forward for an ECG or to provide blood samples. The same questionnaire was re-administered 30 days following disclosure of results (T30) and, in all cases of confirmed malignancy, at pre-surgical admission (Tpre-op).*
Results: *In this study we examined results on perceived sexual function following transrectal ultrasound guided prostate biopsy for suspected neoplasia. Eighteen of the 240 consecutive patients suitable for the study were excluded due to their inability to reliably complete the IIEF-15 questionnaires provided. Histological results led to the selection of 98 patients (44.1%) with neoplastic pathology, group A, and 124 (55.8%) with benign pathology, group B. At T0 a normal level of erectile function was evident in 50 group A patients (51%) and in 50 group B patients (40.3%), while ED has been reported in 48 individuals (49%) in group A and in 74 (59.7%) in group B. At T30 we observed in group A a decrease of the mean IIEF-15 score from 53.6 to 37.8 ($p = 0.0013$). We observed similar results in group B, where 10/50 patients developed ED with a consequent reduction of the IIEF average score from 55.9 to 48.3 ($p = 0.04$). Of the 16 patients in group A who developed ED after biopsy only 2 were eligible for surgery and there were no statistical differences in the IIEF scores comparing T30 with T-pre-surgery ($p = 0.36$).*
Conclusions: *In this study, as previously documented in literature, no direct correlation was observed between ED in patients and the diagnosis of prostate cancer. The only seemingly correlative factor between ED and prostate cancer is biopsy itself. Further specific studies should be carried out to assess whether ED is a psychological result of an emotional stressful event or whether resulting physical damage following the biopsy procedure is to blame.*

KEY WORDS: *Erectile function; Prostate biopsy.*

INTRODUCTION

Erectile dysfunction is one of the primary complications of all treatments for prostate cancer and amongst those which affect patients' well being post-treatment most. The introduction of nerve-sparing surgery has only gone part of the way in resolving the problem, so for this reason in more recent years, and in an aim to improve the quality of life of patients, attempts have been made to address erectile deficit using intracavernous injection therapy with PGE1 (Alprostadil) or by prescribing 5-phosphodiesterase inhibitors (Sildenafil, Tadalafil, Vardenafil). Though much

emphasis is placed on erectile function following the treatment of prostate cancer, insufficient research has been carried out into erectile function pre-treatment. Existing literature on the subject tends to divide patients into two groups: those who have so far not experienced erectile problems, and those who suffer from erectile dysfunction. Patients are normally divided into their respective groups upon answering either a simple series of questions or a pre-set questionnaire, or upon completing an IIEF-15 just after surgery on their sex life during the four weeks leading up to the procedure. The treatment delay: time lapsed between prostate biopsy and disclosure of cancer diagnosis and communication of the chosen treatment method was 4 weeks.

In a prospective study carried out on 211 patients undergoing prostate needle biopsy, *Zisman et al.* reveal that 64% of patients reported preoperative anxiety lasting from several days before the procedure until the disclosure of cancer diagnosis (1). In addition, of those patients who had previously reported normal erectile function pre-biopsy, 7% complained of difficulty in achieving an erection sufficient for sexual intercourse in the days leading up to the biopsy, and up to 15% of patients reported ED in the period immediately following the biopsy until the disclosure of cancer diagnosis.

These results suggest that the sex life of those patients due prostate cancer treatment cannot be assessed simply based on information taken in the period immediately preceding or following surgery, but instead should be studied at each step of the treatment process.

This study is intended to assess variation of patient's sexual function at different treatment stages with the aid of a validated questionnaire. The questionnaire covers the period before carrying out prostate biopsy, including the disclosure of post-surgery histological examination of the tumour, and the post-surgery recovery period. The control group consisted of patients with benign prostate lesions.

Materials and Methods

240 patients who were to undergo trans-rectal ultrasound guided prostate biopsy due to suspected prostate cancer were consecutively studied prospectively between January 2008 and January 2009. All patients were studied according to their medical and sexual history, laboratory examinations, and a new PSA dosing regime. All biopsies were performed using the same standard sextant biopsy technique and all employed an automatic tru-cut core needle throw with 22 mm excursion. Oral anticoagulant therapy was substituted with low molecular weight heparin injections for seven days preceding surgery and 7 days following it, and in all cases adequate fluoroquinolonic antibiotic treatment was recommended from the night before surgery.

Patients were asked to complete a IIEF-15 questionnaire to assess sexual function during the initial consultation (T0), generally whilst they waited to be called forward for an ECG or to provide blood samples. The same questionnaire was re-administered 30 days following disclosure of cancer results (T30) and, in all cases of confirmed malignancy; it was administered yet again following pre-surgical admission (Tpre-op).

Statistical analysis of the IIEF-15 questionnaire was carried out using student t-test for both paired and unpaired data.

Results

In this study we have examined results on perceived sexual function following transrectal ultrasound guided prostate biopsy for suspected neoplasia. 18 of the 240 consecutive patients suitable for study were excluded due to their inability to reliably complete the IIEF-15 questionnaires provided.

During the disclosure of diagnosis, around ten days following the biopsy, and during the successive follow-up thirty days later no patient had complained of severe side effects requiring re-admission or medical treatment following the surgical procedure.

Histological results led to the selection of 98 patients (44.1%) with neoplastic pathology, group A, and 124 (55.8%) with benign pathology, group B. The average age across the population studied (aged 51-92) was 70.3 years. 96 patients in group A were diagnosed with prostatic adenocarcinoma, and 2 patients were diagnosed with tumour infiltrating urothelial carcinoma. 68 patients in group B were diagnosed with benign prostatic hyperplasia, 52 were diagnosed with IPB and prostatic flogosis, and 4 had just flogosis. The group A average age as was 71.9 years (patients aged 51-87), the group B average age was 70.3 years (53-92): both groups produced homogenous results across age distribution.

In both groups, factors for ED were taken into account, such as diabetes, hypertension, pre-existing cardiovascular disorders, smoking and LUTS. All patients who complained of lower urinary tract disorders were already undergoing treatment with alphalitics or finasteride. The distribution of risk factors in patients across the two groups is displayed in Table 1. The main differences between group A and B can be observed in the use of alphalitics (22.4 vs 62.9%) and finasteride (4 vs 25.8%). The average prostate volume in the neoplasia group and benign tumours, measured in cubic cm by TRUS through three major axes (anterior-posterior, latero-lateral, cranial-caudal), was 36.4cc (range: 15-70) and 50.33 (range: 15-108) respectively. Significant differences between the two

Table 1.
Risk factors betwwen patients with neoplastic (Group A) and benign pathology (Group B).

	Group A (n = 98)	Group B (n = 124)
Average age	71.9	68.7
Diabetes mellitus	14 (14.3%)	30 (24.2%)
Hypertension	68 (69.4%)	68 (54.8%)
Cardiovascular disease	24 (24.5%)	26 (37.1%)
Smoke	30 (30.6%)	32 (25.8%)
Alpha-lytics	22 (22.4%)	78 (62.9%)
Fynasteride	4 (4%)	32 (25.8%)

groups were evident when examining average third-generation PSA (24.2 vs. 7.4) and free PSA (12.8 vs. 19.6); in the first group 96/98 patients had PSA values > 3.5 ng/ml, compared with 102/124 patients in the second group.
In group A, 58 patients (59.2%) had suspected cancer based on the TRUS and the same number of patients had presented nodular areas during the digito-rectal exploration. In group B, prostate cancer was not evident when carrying out TRUS or with DRE, in 120 (96.8%) and in 114 patients (91.9%) respectively. In this study we considered several cases of re-biopsies: 20 patients (20.4%) in group A and 40 patients in group B (32.3%).
Whilst recording patient medical history we evaluated sexual and erectile function comparing the score of the IIEF-15 questionnaire with the initial consultation, T0. Only in 2/222 cases did we observe a complete correlation of results. Conforming with the parameters introduced by *Rosen et al*. (2) we divided the two principal groups into two further sub-groups according to the IIEF-15 scores; those suffering from ED and those not. A normal level of erectile function was evident in 50 group A patients (51%) and in 50 group B patients (40.3%), while ED has been reported in 48 individuals (49%) in group A and in 74 (59.7%) in group B. In group A, the IIEF-15 medium score result was 53.6 in the sub-group of patients without ED, and 11.7 in patients with ED; in group B these values were 55.9 and 10.8 respectively.
One month after communicating histological diagnosis, all the patients enrolled in the study answered the IIEF-15 questionnaire once again. Substantial differences in the questionnaire scores were not noticed in those patients presenting ED before the biopsy (11.7 vs. 11.9 in group A; 10.3 vs. 13.3 in the group B).
Noticeable differences have been recorded in those cases where normal sexual function existed before the biopsy. In group A, 16/50 patients show a decline in their sexual function when comparing results from the IIEF-15 and T0, (12 patients reported severe ED and 4 moderate ED), resulting in a decrease of the medium IIEF-15 score from 53.6 to 37.8 ($p = 0.0013$). We observed similar results in group B, where 10/50 patients developed ED with a consequent reduction of the IIEF average score from 55.9 to 48.3 ($p = 0.04$). The analysis of the IIEF results at T30 has not shown differences statistically significant between the two groups highlighting that ED arose after the biopsy is not correlated with the histology results.
Of the 16 patients who developed ED after biopsy only 2 were eligible for surgery and there were no statistical differences in the IIEF scores comparing T30 with T-pre-surgery ($p = 0.36$).

Discussion

The aim of this study is to evaluate variation in erectile function in patients suspected of having prostate cancer during different phases starting from the biopsy to treatment through to communication of the histological results. In this prospective study we have analysed the IIEF-15 questionnaires completed by patients 30 days before the biopsy, 30 days after the communication of the histological response, and for those patients eligible for the surgical treatment a further questionnaire was completed in the immediate pre-operative period.
During the period considered the only two factors potentially responsible for any changes in the patient's quality of life and their erectile function were the biopsy and the final diagnosis. With regards to the biopsy, several studies have researched the most common complications. *Rodriguez et al.* (3) show in their experience pain and vagal crisis during the procedure, emospermia and sepsis but they do not refer to aspects potentially involved in the sexual sphere such as perineal and rectal nuisance or anxiety preceding or following the biopsy. These aspects are considered by *Zisman et al.* (1) in their prospective study on 211 patients. Anxiety was present in 64% of patients before the procedure and this percentage reached 75% during the 7 days following the biopsy, probably due to the waiting of the diagnosis.
Of 54 patients diagnosed with malignant cancer, 74% suffered persistent anxiety during the month after biopsy, compared to 15% of patients with benign pathology. Of the 168 patients who did not suffer from ED before the biopsy 42 (25%) reported the presence of erectile dysfunction in the first week following the biopsy, and in 21 patients the problem persisted for one month after the procedure, even if only 7 patients received a diagnosis of malignancy. The authors report that in 7 cases ED arose in the moment patients discovered they required a prostate biopsy and this condition resolved itself in 3 patients following the execution of the exam. This data shows the correlation between anxiety and ED but not between ED and histological diagnosis.
In our study 122/222 patients (54.9%) suspected of having cancer based on clinical, ultrasound or laboratory evaluations presented ED. The two groups built on the basis of presence or absence of cancer presented a similar distribution of risk factors for erectile dysfunction with the exception of the greater use of finasteride and alpha-blockers in patients with benign prostatic hyperplasia.
A second IIEF-15 questionnaire was completed one month following disclosure of the histological exam with the aim of excluding the anxiety the waiting period between the biopsy and results has on erectile function. This decision comes from evaluating the results presented by *Gustaffson et al.*, in a study which considers the psycho-physiological reaction in patients with suspected prostate cancer. The authors show how the plasmatic cortisol level, associated with psycho-physiological stress, increased evidently with the suspicion of prostate cancer before the communication of the histological diagnosis and decreased after this communication independently from its result (4).
In the population studied, which was divided based on the histological diagnosis made, 16/50 (32%) of patients in group A and 10/50 (20%) of patients in group B developed ex novo erectile dysfunction following the prostate biopsy. This data supports the idea that the onset of erectile dysfunction is not correlated with the kind of diagnosis as already shown by *Zisman et al.* (1). Those authors underlined that erectile dysfunction could be correlated with the direct damage of the needle on the neurovascular bundles or indirectly with the

compression on this structures by subclinical oedemas and haematomas. In this study, and in evidence already documented in literature, no direct correlation has been observed between ED in patients and the diagnosis of prostate cancer (5). In the population of patients with prostatic neoplasia reporting ED following the biopsy, a greater prevalence of negative prognostic factors was observed compared with other patients with diagnosis of cancer who did not develop ED. 30/34 (88%) of patients who did not develop erectile dysfunction were eligible for surgery due to localised disease, whilst of the 26 patients with ED only one could profit by this treatment. Of the patients without erectile dysfunction the average Gleason score value was 6.9 and PSA was major than 10 ng/ml only in four cases; on the contrary in the group of patients who developed ED the average value of Gleason score was 8 and the PSA value was minor than 10 ng/ml only in 2 cases.

Conclusion

In this study, and in evidence already documented in literature, no direct correlation has been observed between ED in patients and the diagnosis of prostate cancer (5). What has arisen from the study is that a small fraction of patients treated for prostate cancer begin to suffer from ED following biopsy despite not reporting the problem before the procedure.
ED does not seem to be directly correlated to the diagnosis of prostate cancer as it also presents itself in patients with benign prostatic hyperpalsia.
One interesting piece of data, which would require further study involving more subjects in order to be confirmed, is the correlation between a worst diagnosis and the onset of erectile dysfunction.
The only seemingly correlative factor between ED and prostate cancer is in the biopsy itself.
Further specific studies should be carried out to assess whether ED is a psychological result of an emotional stressful event or whether resulting physical damage following the biopsy procedure is to blame.

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PRESENTATION

Elastosonography in the Peyronie's disease: Our preliminary experience.

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Summary

This work aims to inform our experience on a new diagnostic method applied to Peyronie's disease. Our study demonstrates that real time sonoelastography is more reliable than traditional ultrasound because it can detect all palpable plaques, evaluating precisely the thickness, size, involvement of surrounding tissues. These features can be also assessed a flaccid penis.

KEY WORDS: *Peyronie's disease; Elastosonography.*

INTRODUCTION

Peyronie's disease (induratio penis plastica) is surely the penile disease in which the U.S. (1-5) is the major directions and practicalities of implementation. The survey ultrasound can detect the location, number, extent and density of plaques. The major limitation of this technique is that only 40% of palpable plaques can be detected by ultrasound traditional. U.S. (8) pattern is also highly variable shapes ranging from hypoechoic to hyperechoic forms with or without posterior acoustic barrier (6-7).
The elastosonography (2) is a recent ultrasound technique that enables better tissue characterization. The elastosonographic image is the consequence of mechanical properties/elastic tissue by ultrasound path and under a pressure perpendicular. Different levels of elasticity of the tissues that have suffered during the pressure run with the probe, forming a more or less relevant using a color scale are assessed (3-4).
The study reports our experience in the use of real time sonoelastography in Peyronie's disease.

MATERIALS AND METHODS

From January 2009 to June 2010 we submitted 45 patients with Peyronie's disease with ultrasound integrated through elastosonography penile conditions flaccidity and erection drug-induced (10 mgr PGE1). The instrument used is the Hitachi ultrasound Logos Vision implemented with II generation elastosonography. Were assessed the position, length, thickness, involvement of surrounding tissue, the septum intercavernosum and rigidity of the plaques.

RESULTS

The elastosonography identified all the plaques present (59), while the traditional ultrasound has identified 26, also found a length, a width and a greater involvement of surrounding tissues than those assessed by ultrasound, in addition we assessed the sonoelastographic characteristics in erection and flaccidity that finding no significant differences in the plaque.
The average age of patients was 53.08 years with a range running from 32 at 75 years, the 26 plaques identified with traditional ultrasound had an average length of 2.72 cm with a maximum length of 3.8 cm minimum of 1.5 cm and the average thickness of 0.51 cm was observed with a maximum thickness of 0.7 and a minimum of 0.3 cm, while the 59 plaques elastosonography highlighted in real time had an average length of 2.48 cm with a maximum length of 4.1 cm and 1.4 cm minimum average thickness was 0.52 cm with a maximum thickness of 0.8 cm and a thickness of 0.3 cm. The traditional ultrasound revealed the involvement of the septum intercavernosum in 5 cases and 8 cases in real time elastosonography. Fibrosis of the corpora cavernosa to the underlying plaque was detected in 3 cases in conventional sonography while 13 cases in real time elastosonography.

Conclusions

The elastosonography in real time is an imaging technique that is very reliable as unable to detect any palpable plaques and assess accurately the thickness, size, involvement of surrounding tissue and septum intercavernosum (very important for the possible surgery). Conventional ultrasound performed at the same time, it takes time and costs. Instead there is an additional time savings for the operator saw negligible differences in the assessment of plaque size between flaccid and erect penis drug induced.

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PRESENTATION

Color Doppler ultrasonographic scanning in acute bacterial prostatitis.

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Summary

Objectives: *The purpose of this study was to reveal parenchymal and vascular changes in acute prostatitis and to determine the role of color Doppler sonography in monitoring patients with this pathology.*

Material and Methods: *Twenty five patients with a clinical diagnosis of acute bacterial prostatitis (NIH 1) admitted to our institution were studied prospectively. Clinical, analytical and microbiological data were recorded. Color Doppler and transrectal ultrasonography (TRUS) were performed 1 week after antibiotic therapy and afterwards at 6 weeks, 3 and 6 month visits. The findings were recorded and scored using standardized criteria to characterize the degree and distribution of prostatic vascularity.*

Results: *Blood flow was observed to the entire prostate capsule (grade 2) in 23 (92%) patients at first visit (1 week) and were present in 11 (44%), 6 (24%) and 2 (8%) at 6 weeks, 3 and 6 month visits respectively. The amount and distribution of blood flow within the prostatic parenchyma were evaluated using several criteria. Using the 2-point scale flow were classified as grade 2 22 (88%), 18 (72%), 12 (48%) and 3 (12%) patients at first, second, third and fourth visit respectively. Similar findings were noted using the Doppler spot scale which revealed that flow was grade 2 (15 spots or more) in 23 (92%), 19 (76%), 11 (44%) and 3 (12%) patients respectively. Mean number of Doppler spots in the prostate parenchyma was 23.1 ± 11.1 at first visit, 10.3 ± 9.5 after the end of therapy and 8.3 ± 5.4 and 7.9 ± 5.1 at 3 and 6 monthly respectively.*

Conclusions: *Patients with acute prostatitis require prolonged treatment and subsequent follow up for at least 6 months. Color Doppler sonography is a useful tool in monitoring response to treatment and in predicting clinical outcome.*

KEY WORDS: *Transrectal ultrasonography; Color Doppler; Acute bacterial prostatitis.*

INTRODUCTION

The prevalence of prostatitis in the general population is estimated at 12%, and is considered the most common urological diagnosis in men younger than 50 years (1). Traditionally the diagnosis and management of acute bacterial prostatitis depends on the clinical and laboratory assessment, these results may be subjective and lead to underdiagnosis of this entity, especially in cases that presents with a clinical picture of moderate or low intensity, which have their clinical and therapeutic implications on the management of the patient (2, 3). The value of prostatic transrectal ultrasound (TRUS) is controversial in patients with acute bacterial prostatitis, and is only indicated in the exclusion of prostatic abscess. The advent of Doppler allows the evaluation of blood flow, however, the only finding described in the literature up to now is a nonspecific increase of the Doppler signal in the prostatic peripheral zone (4). In this study we evaluate the vascular and parenchymal changes of the prostate in acute prostatitis, trying to define evaluation criteria to enable the monitorizacion of patients with this pathology.

MATERIAL AND METHODS

Were involved in this study, 25 male patients with a mean age of 38 years (between 22-50 years old) admitted to our hospital with the clinical diagnosis of acute bacterial prostatitis (NIH category I). All patients underwent a medical history, physical examination and analytical evaluation (white blood count, prostate-specific antigen (PSA), urine II, and urine cultures). Acute bacterial prostatitis was defined as lower urinary tract symptoms with fever (axilary temperature > 38ºC) and tender prostate at rectal

examination and/or PSA > 10 ng/ml with positive urine culture (> 105 cfu/ml) for a uropathogen.
Patients were treated with intravenous Ceftriaxone until defervescence with clinical improvement, followed by treatment with ofloxacin 200 mg twice daily for 6 weeks.
TRUS with color Doppler was performed after 1 week of antibiotic therapy and afterwards at 6 weeks in the end of therapy and at 3 and 6 months. The TRUS was performed by the same physician, using a *Voluson 730 Expert* (*General Electric Medical Systems*) with a 5-9 MHz. endfire transrectal lineal probe. Patients were approached in the left lateral decubitus position.
Color Doppler sonography was optimized. The pulse repetition frequency was 1.000 Hz and overall color gain was set just above the noise threshold. The high pass filter was lowered to 15 Hz and color write priority was maximized.
Representative images were recorded at each of the 3 ultrasound defined zones in the transverse plane (apical prostate apex, mid prostate and prostate base). Images representing the maximum demonstrable flow were recorded for each zone.
Findings were recorded according to standardized criteria, using a 2 point scale to characterize the degree of vascularity in the prostatic capsule and parenchyma (Appendix 1). In addition, we counted the number of Doppler spots and considered the distribution of those Doppler spots as focal or diffuse. The Doppler spot scale was also classified as grade 1 (less than 15 points) or grade 2 (15 points or more).
We used the SPSS 11.5 statistical model to evaluate, analyze and compare the data obtained.

Results

Of the 25 patients diagnosed with acute bacterial prostatitis, 12 (48%) reported previous infections of the urinary tract. The average duration of fever was 1.5 ± 0.7 days before diagnosis. Nineteen (76%) patients had perineal pain or discomfort and 22 (88%) had a tender prostate at rectal examination.
The mean admission serum PSA level was 19.3 ± 11.3 ng/ml. After 6 weeks, at the end of antibiotic therapy, the median PSA was 5.3 ± 7.6. All patients except two had at this time PSA < 10 ng/ml. Six (24%) patients had a PSA between 4 and 8 ng/ml and the remaining 17 (68%) had a PSA < 4 ng/ml.
Urine culture was positive for Escherichia coli in 19 (76%) patients. The other agents were Proteus mirabilis, Klebsiella sp., Enterococcus faecalis, Pseudomonas aeruginosa and Enterobacter sp .. All patients had clinically and bacteriologically remission, just one case of recurrence during the follow-up.
The mean prostatic volume in the first assessment was 40.5 ± 17.9 ml. Eleven (46.6%) patients had sonographic lesions in peripheral prostatic lobules [unilateral hypoechoic lesion in 3 (12%), bilateral hypoechogenic lesion in 2 (8%), unilateral hyperechoic lesion in 4 (16%) and bilateral heterogeneous lesion in 2 (8%)]. No prostatic abscess were detected. Six weeks after this assessment, at the end of antibiotic treatment, these lesions regressed or disappeared in 61.1% of patients, and the mean prostatic volume was 24.3 ± 10.5 ml. Absence of significant variations in terms of mean prostatic volume on 3 and 6 months assessments.
Blood flow was observed over the entire length of the prostate capsule (grade 2) in 23 (92%) patients in the first assessment (1 week), present in 11 (44%), 6 (24%) and 2 (8%) at 6 weeks, 3 and 6 months respectively. The volume and distribution of blood flow in the prostatic parenchyma was evaluated using multiple criteria. Using the scale of two values, the flow was classified as grade 2 in 22 (88%), 18 (72%), 12 (48%) and 3 (12%) patients in the first, second, third and fourth draft assessment respectively. Similar findings were recorded using the Doppler point scale, which revealed grade 2 flow (15 or more points) in 23 (92%), 19 (76%), 11 (44%) and 3 (12%) patients respectively. The mean number of points in the Doppler prostatic parenchyma was 23.1 ± 11.1 in the first evaluation, 10.3 ± 9.5 at the end of antibiotic treatment and 8.3 ± 5.4 and 7.9 ± 5.1 to 3 and 6 months respectively.
There were no episodes of urosepsis after manipulation with the ultrasound probe during the acute phase of infection.

Discussion

The evaluation and the diagnostic management of acute bacterial prostatitis is well defined in worldwide accepted *National Institutes of Health* (NIH) classification for prostatitis syndromes (5). In patients with symptoms of acute bacterial prostatitis (NIH category 1) urine culture is considered the only laboratory evaluation of the lower urinary tract that is required. And a possible sonographic evaluation of the prostate only to exclude a prostatic abscess.
Some previous studies describing the sonographic findings of acute bacterial prostatitis, including an increased volume of the prostate, a global hipoechogenicity of the gland, a hypoechoic zone around the urethra and peripheral focal hypoechoic lesions (6-9). This study detected sonographic lesions at the peripheral lobules in approximately half of the patients involved, and an increase in prostate volume in most patients. These lesions disappeared or decreased after antibiotic therapy in two thirds of patients and the volume has decreased overall. The color Doppler ultrasonography has some limited features, it is more subjective and operator dependent than standard gray scale ultrasonography (10, 11, 12), hence the need and importance of this study in an attempt to quantify the sonographic findings. There is no consensus about the optimal technique for the TRUS with color Doppler, because color Doppler signals vary shades of the color spectrum depending on the direction and speed of flow. The operator dependent and independent parameters such as color gain, the pulse repetition frequency and the wall filter settings, influence the quality image quality.
In this study we tried to minimize these variables by defining and setting the parameters of work in order to allow the reproducibility of the same, and all examinations were performed by the same physician.
There is no agreement on the optimal scheme for classifying color Doppler images of the prostate. Some recom-

mend a variety of criteria to delineate scales with 3 (13, 14) and 4 (15, 4) degrees. Each of these grading systems has a high degree of intra-observer variation. After the study of different classification schemes, we chose to build one, which has a scale with a smaller number of degrees, that would be less subjective in its application, and more easily interpretable and therefore reproductable. In this study we observed that the infectious process of acute bacterial prostatitis is reflected by ultrasound by a diffuse increase of prostate vascularisation, both in the capsule or in parenchyma. There is a relationship between the clinical improvement during the antibiotic therapy and the decrease of vascularisation degree. Noted that even after 6 months of follow-up exists in some patients an increased vascularity that can translate the presence of residual foci of infection.

Conclusion

Patients with acute prostatitis require prolonged treatment with a subsequent follow up at least six months. The use of color Doppler sonography is a valuable tool in monitoring treatment response and prediction of clinical outcome.

APPENDIX 1

Color Doppler scoring of prostatic blood flow.

Anatomical Site	**Blood Flow**
Prostate capsule	
Grade 1	Nonvisualized or sparse
Grade 2	Complete or in all extension
Prostate parenchyma	
Grade 1	Nonradiating flow, short segments of vessels
Grade 2	More than 1 radiating vessel penetrating parenchyma
Prostate parenchyma Doppler spot scale	
Grade 1	Less than 15 points
Grade 2	15 points or more
Doppler spots distribution	
Focal	
Diffuse	

Figure 1.
Capsular flow grade 2 and parenchymal flow grade 2.

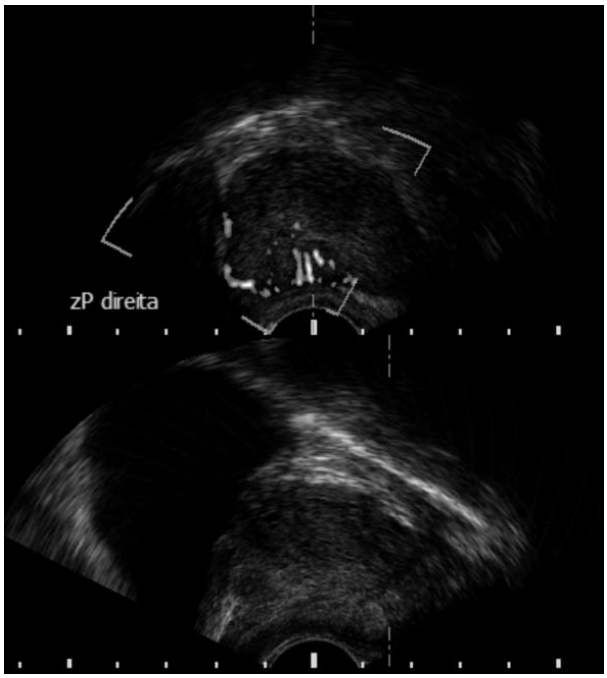


Figure 2.
Doppler spot grade 2 difuse.

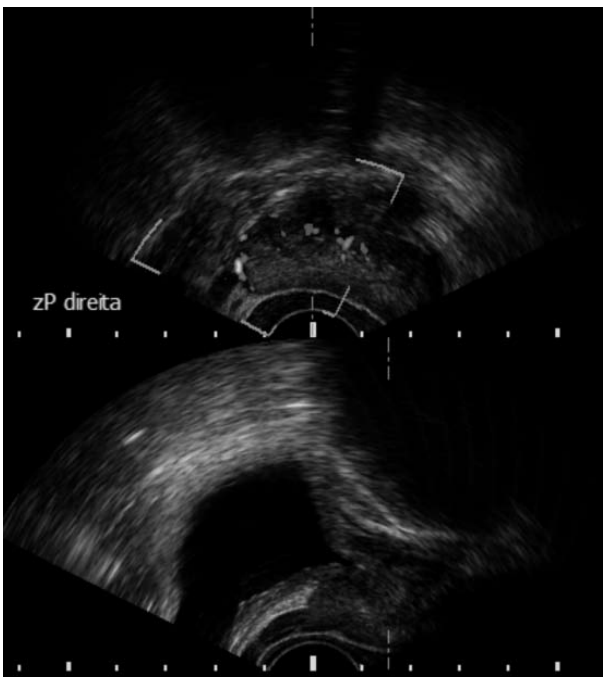
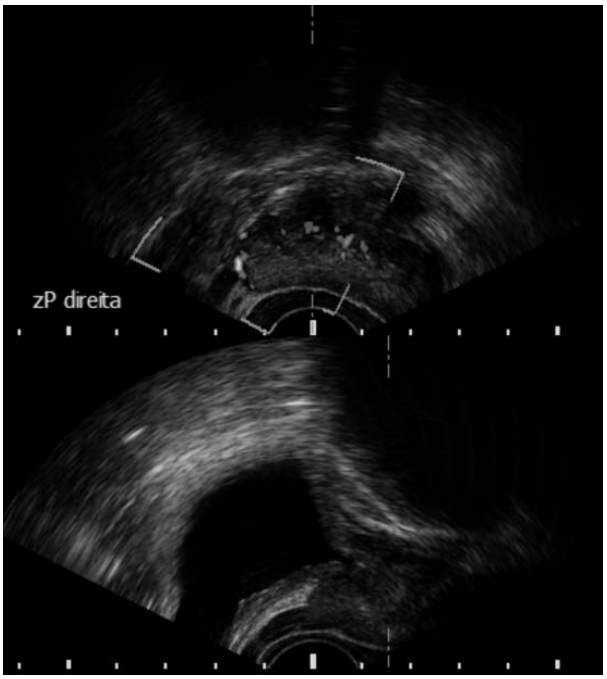


Figure 3.
Doppler spot grade 1 difuse at 6 weeks.



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PRESENTATION

The role of color Doppler in acute kidney injury.

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Summary

In recent years, echographic studies of the kidney have improved radically due to new technologies which have recently become available. Among these, perhaps the most useful one is the ultrasonographic (US) procedure for the simultaneous laboratory and clinical workup of patients affected with acute nephropathic syndromes.

However, traditional B-mode ultrasonography lack of sensibility and specificity in identifying and evaluating Acute Kidney Injury (AKI) is well known.

Although the most objective measure in the study of different nephropathies remains by far the biopsy, several studies have indicated the usefulness of combining the B-mode ultrasound (US) with echo-color Doppler as a tool in determining intrarenal parenchymal arteries in the for differential diagnosis and predicion of clinical outcomes.

In fact, the resistivity index (RI), determined by the formula: IR = (peak systolic velocity) – (end-diastolic or telediastolic velocity)/(peak systolic velocity) can be, after proper technical correction, easily measured at the level of the arcuate arteries or at the interlobar arteries. The final value is the average of 3-5 peaks, consecutively determined for each kidney at the upper pole, in the mesorenal area and also at the lower pole. The variation in normal IR values is ≤ 0.70 with the difference diminishing progressively from segmental to interlobar vessels. Acute Kidney Injury (AKI) is perhaps one of the most important areas for the application of the Resistivity Index (RI). The differential diagnosis between prerenal AKI (which is functional and reversible if the cause of hypoperfusion is corrected) and renal AKI (which is organic and mainly caused by tubular necrosis (ATN) or acute interstitial nephritis) is facilitated by measurements of the RI, in addition to the normal clinical laboratory and clinical data. In fact, most prerenal AKI patients show normal parenchymal vascular flow, with RI < 0.70, whereas those with AKI due to NTA have a reduced parenchymal perfusion, accompanied by elevated RI values, prior to any evidence of abnormal values of creatinine or of oligoanuria. Follow-up of patients with both renal and prerenal AKI by serial monitoring of RI during medical treatment of AKI shows a progressive reduction and ultimately the normalization of RI values of renal parenchymal vessels and often precedes the return to normal kidney function.

In post-renal obstructive AKI patients, absolute values of RI > 0.70 on the obstructed kidney and a RI difference (ΔRI) between the two kidneys of > 0.06-0.08 are considered diagnostic of an obstruction. Elevated values of RI are also considered useful in the diagnosis of hemolytic-uremic syndrome (HUS) and are a significant predictor of prognosis: the normalization of IR precedes the return of normal renal functionality. Similarly, measurement of RI in patients with liver disease and normal renal function may help in early detection of latent hepato-renal syndrome. Although the IR is not, strictly speaking, a measure of renal function it may nevertheless be correlated with it especially if elevated arterial resistivity is accompanied by a reduction in renal function itself. Thus, IR may be considered a useful predictive index in specific clinical settings.

KEY WORDS: *Echo-tomography; B-mode US; Imaging; Prognosis; Renal function.*

INTRODUCTION

Echo-tomography of the urinary tract represents an important diagnostic tool for studying patients with Acute Kidney Injury (AKI). Morphological evaluation of the kidneys and urinary tract using B-mode ultrasonography (US) allows the identification of patients with chronic renal disease. This is manifest echo-tomographi-

cally as small "end-stage" kidneys, and can be distinguished from those patients with AKI in which the parenchyma is intact but swollen and echogenically normal or enhanced or those with obstruction of the urinary tract and requiring surgery. This test offers the advantage of being rapid and non-invasive with good test-re-test reproducibility and a low cost so that strategies for treatment can be easily and rapidly oriented with respect to AKI as well as to predict the prognosis of the patient. The advent and rapid development of the technologies using echo-color Doppler has facilitated an accurate picture of the renal vascular bed in general and in particular, for pathological conditions such as AKI, the measurement of important resistance parameters in the arterioles of the renal parenchyma. This can furnish valuable information about the acute syndrome in course.

Evaluation of various forms of AKI using B-Mode US

Functional or prerenal AKI generally is resolved rapidly and reversibly within 24 to 48 hours, if an appropriate therapy is applied to deal with the cause of this condition. From a pathophysiological point of view, this condition originates in a renal hypoperfusion due to various causes. Up until now, a diagnosis was based essentially on a careful anamnesis and accurate objective clinical and laboratory tests. In fact, since renal injury is functional and thus potentially reversible, the ultrasound picture is non-specific, with outcomes within normal values for both size and volume as well as echogenicity of the renal parenchyma.

In those cases when renal ischemia may be severe or prolonged, functional or prerenal AKI may be transformed into renal AKI, which is manifest as acute tubular necrosis (ATN) in its most frequent and characteristic form. The results of ultrasonography may be non-specific and similar to many other acute pathologies involving the kidney such as increased renal volume, normal echogenicity of the parenchyma or more frequently, a diffuse increase in echogenicity in comparison with adjacent organs like the spleen or liver as a result of reduced vascular perfusion. Such finding is more common in tubulo-interstitial disease rather than glomerulopathies (1-3). Frequently, dilatation of the renal pyramids is seen with clear demarcation of the pyramid probably due to interstitial edema. Volume increase in the anterior-posterior (A-P) diameter of both kidneys is often seen but the longitudinal axis (L) is normal value for (4). The ratio of the A-P diameter to the L-diameter (AP/L) is considered normal for values of 0.45 ± 0.04, but in patients with ATN not only is the A-P/L ratio significantly increased to > 0.53 but it is also directly proportional to creatinine values and serum potassium and inversely proportional to urinary osmolarity. It must be remembered that urinary osmolarity is an important indicator of tubular integrity and in a routine workup of the differential diagnosis, in functional AKI urinary osmolarity is > 500 mOsm/kg H_2O while renal AKI has osmolarity values of < 350. Besides this, the A-P/L ratio might be a valid prognostic indicator of NTA since patients with a statistically significant increase in this ratio would require a longer time (on average 32.4 days) to improve and thus a longer period and a higher number of dialysis treatments in comparison with those having a normal A-P/L ratio (on average 15.5 days) to reach the same level of functionality.

An atypical US finding has been described in oligoanuric patients with AKI associated with the use of a non-steroid anti-inflammatory drug (NSAID) (5), with rhabdomyolysis (6), with severe hypotension (7), and severe lumbar backpain after intense physical exercise (8). Ultrasonography shows distinctly hypo-echogenic wedge-shaped lesions running from the cortex to the medulla. Pathogenically, it seems that their etiology may be due to a parcellar vasoconstriction causing areas of infarcted tissue. In the initial phases of AKI, computed tomography might document these lesions better and confirm the definitive diagnosis, especially at onset of AKI or when creatinine values have returned to normal. Recently, however, these lesions have been described and documented also in US when this test is carried out during an intermediate phase, when diuresis begins and when the values of creatinemia are in the range of 2 mg/dl (9). Such difference in the timeframe between the visualization of the renal lesions using different imaging techniques would seem to be attributable to the severity of vasoconstriction. The more diffuse and severe the lesions, as at the start of the disease or even in the healing phase, the less efficacious is ultrasonography compared with tomography in identifying the wedge-shaped lesions.

With respect to obstructive AKI or post-renal AKI, echotomography is the diagnostic tool of choice, since it can immediately point to the cause of AKI. US represents an excellent technique for the diagnosis of pyelocaliceal dilatation. In comparison with other imaging techniques such as ECD, urography and nuclear imaging which reveal functional patency, echo-tomography furnishes reliable information about the anatomic state of the urinary tract and thus about a definitive diagnosis of possible obstruction. US represents an excellent first-line tool for defining obstructive AKI with a sensitivity of between 65 to 84% in different case series for initial or non severe dilations and of about 90% in case of severe hydronephrosis (10-12). In the case of mild or moderate hydronephrosis (grade I-II), echoes in the renal sinus appear distinct from those originating from the distension of the calyx and the renal pelvis. These appear as multiple or peripheral anechogenic areas separated from the central zone. In grade I hydronephrosis, careful scans along the longitudinal lateral or coronal, longitudinal oblique posterior or transverse areas may reveal a typical joining of these anechogenic areas. Such a finding is pathognomic of dilation and consents a differential diagnosis from a para-pyelic cyst or mass (12).

When hydronephrosis is more marked, as in grade II, the echoes from the renal sinus increase, thus highlighting the pyelo-calyceal joint. In grade III-IV hydronephrosis, dilatation of the pyelocalyx is extensive resulting in pronounced finger-like projections of the calyx in the image. In extreme cases, it is possible to see a single anechogenic sac with reduction or total disappearance of the parechyma and highlighting of the upper third of the ureter. This is the typical picture of hydroureteronephrosis.

Evaluation of AKI using EchoColor Doppler (ECD)

Doppler studies of small intra-renal vessels require a discrete technical competence to achieve reliable information. So far, most studies have concentrated attention on distal intra-renal vessels such as segmental, interlobar or arcuate vessels with specific attention to the corticomedullary junction and along the edge of the medullary pyramids. One study carried out on patients with normal renal function revealed that that the Resistivity Index (RI) is more reliable if the measurements are taken at the interlobar and arcuate arteries (13). These small blood vessels normally have a low velocity of flow and thus small shifts of frequency. Careful attention to technical procedures when measuring these small shifts include setting the lowest possible value for the Doppler filter and the use of a small range of repeated pulse frequencies of impulse or Pulse Repetition Frequency (PRF) to avoid the phenomenon of "aliasing". The resistive index (RI) is easily calculated automatically and is given by the equation

$$IR = \frac{\text{(peak systolic velocity)} - \text{(end-diastolic or telediastolic velocity)}}{\text{(peak systolic velocity)}}$$

This parameter is a true reflection of renal artery resisitivity and a significant correlation between RI and the renal vessel resistivity has been repeatedly confirmed (14). It must be emphasized that RI itself is not an index of renal function but only a measure of the renal vascular resistance. However, it is obvious that in the presence of an altered renal function, an altered renal RI is a reliable indicator of altered renal functioning. On the other hand, there are nephropathologies which significantly jeopardize renal function without significantly changing the RI. In such cases, RI does not reflect loss of renal functioning.

The importance of determining the RI by ECD in native kidneys rests in the predictive value in specific clinical settings (15). Most researchers agree that a RI of 0.7-0.75 should be considered the maximum normal intrarenal RI (15, 18). Certain conditions may also alter the RI value such as severe hypertension or heart disease, perirenal or subcapsular edema, which tend to increase RI. An elevated RI, considered to be non-pathological, is also present in neonates and children (19).

Recently several studies have been carried out on the use of ECD in Acute Kidney Injury (AKI). In addition to the morphological information obtained by using B mode US, ECD evaluates alterations in renal vessel function, furnishing important information regarding renal function and allowing to differentiate between otherwise indistinguishable forms of AKI. In rabbits, studies have shown that experimentally induced reversible AKI is accompanied by a reduced renal blood flow due mainly to intra-renal vasoconstriction (20). This altered vascular impedence, measured using ECD was prevalent in the early stages of AKI was accompanied by an increase in RI, which reached a maximum value within 12 hours after induction and disappeared completely after 1 week. Creatinine values, on the other hand, were at their highest after 24 hours and returned to normal after no less two weeks. The alteration of RI was precocious and preceded the increase of creatininemia itself. Several neurogenic or humoral mechanisms have been suggested as being implicated in the elevated arterial resistivity in ATN (21).

These experimental data have been confirmed by clinical studies such as that by Platt on patients with AKI, which highlighted the fact that only in 11% of cases were the aforesaid morphological changes to the renal parenchyma present and that these were non-specific in nature whereas in well over 69% of patients, there were renal hemodynamics changes and in particular elevated RI values (22). In 80% of patients with prerenal AKI although parenchymal blood flow is normal or slightly elevated, but the RI value remains normal, ranging from between 0.7 to 0.75. Instead, among those patients with ATN, EchoColor Doppler (ECD) of the renal vessels reveals a marked variation in blood-flow with increased pulsatility and a reduction in peak diastolic flow. Thus, an IR of over 0.75 would be expected in those patients in whom a severe or prolonged form of AKI results in ATN (15). With ECD therefore, the severity and evolution of ATN could easily be monitored. In renal disease, there is a clear association between an elevated IR and a protracted clinical recovery often requiring dialysis. (15). In AKI patients, follow-up studies of ECD sampling during the recovery phase have shown that there is an improvement of blood-flow and RI long before the actual improvement in kidney function and the normalization of serum creatinine (20, 23) become obvious. In the same study (23), complications of AKI caused further variations in ECD values, which returned to normal with full recovery of the patient. It should however be emphasized that ECD is unable to distinguish between the different causes of ATN. For example, variations in velocimetry measurements are seen in sepsis, in marked hypovolemia, in rhabdomyolysis, in ingestion of nephrotoxic substances as well as in Multiple Organ Failure (MOF) (24). More precisely, those pathologies involving the tubular-interstitial tissue and the microcirculation reveal an altered IR, whereas the glomeropathies generally have an IR within normal limits (15).

One recent study has demonstrated the importance of ECD sampling of RI values in the differential diagnosis of functional AKI and ATN, relating RI values to traditional laboratory indices such as fractional excretion of sodium (FeNa), renal failure index (RIF) and the serum/urinary creatinine ratio (Cr ratio) (25). Laboratory data indicative of prerenal or functional ARI are FENa < 1; RFI < 1; Cr ratio > 40, which correlate well with normal RI values, in both the acute and recovery phase of renal functioning. On the contrary, laboratory values indicating an ATN case would be FENa > 1; RFI > 1; Cr ratio < 20, all of which correlate with an elevated value of RI, which return to normal values only when functionality has been restored. In a subgroup of patients with AKI, normalization of IR values actually preceded the return of diuresis and the reduction of creatininemia by some days. The predictive value of Doppler sampling of RI values with respect to the return of renal function suggests serial measurements of this parameter during the entire course of this condition, since RI is not affected by variations of sodium, serum and urinary creatinine due to

diuretic therapy or dialysis. These data are of singular interest since they render an ECD analysis of the renal microcirculation essential in evaluation and differential diagnosis of various forms of AKI.
Hepato-renal syndrome (HRS) is a frequent complication of several hepatic pathologies such as cirrhosis, fulminant hepatitis and neoplastic conditions, and generally appears in an acute form in patients with previously normal renal function. Because such patients do not show evident pathological alteration, HRS is generally classified as a form of functional AKI, even if it is irreversible pathologies, unless of course there is a timely liver transplant. One finding which is almost always observed is a marked intrarenal vasoconstriction (26), thus it is not surprising then that those with these syndromes should present with marked elevated IR values over 0.7-0.75. What is more important is that the hemodynamic alteration is apparent very early on, even before the clinical onset of renal failure and its accompanying rise in serum creatinine (27, 28). ECD can therefore identify liver patients at risk for the developmet of HRS using this simple non-invasive test, thus helping to prevent progression to kidney failure and hepato-renal syndrome. Hepatopathic patients with an RI > 0.70-0.75 have a strong probability of developing a hepato-renal syndrome, with an 26-fold increase in probability as compared with subject having a normal RI (27) thus it is clear that a careful analysis of ECD would help not only those with AKI but would also predict the development of complications of hepato-renal syndrome..
Hemolytic-uremic syndrome (HUS) is a form of AKI which presents essentially in childhood. This thrombotic microangiopathy results in damage to the renal venules and arterioles of medium size and causes a marked vasoconstriction and a consequent increase in intrarenal artery resistivity. It is not surprising then that such patients have a RI which is markedly elevated (29). Clinically, ECD can provide important predictive power about future improvement in kidney failure such that a typical reduction in RI would precede recovery of function and tend to normal values upon full recovery (29). This would allow better planning of therapy or even reduce un-necessary dialysis treatment.
In cases of obstructive (postrenal) AKI, conventional US can furnish anatomical details, mainly regarding dilation of the urinary tract, and may even indicate the entity and level of obstruction. Since dilatation of the urinary tract may be present in non-obstructive AKI, it is important to distinguish between a renal obstruction and non-obstructive dilatation and this may not be possible with only US, which does not furnish information about the physiology or functioning at the site of obstruction itself. ECD can meet these limitations and provide important information about the obstruction (15, 17, 23, 30). Most researchers now believe that hemodynamic alterations such as an elevated vascular resistivity and a marked vasoconstriction may be at the base of renal insult due to an obstruction (31, 32). Thus ECD sampling of RI may be used as a precise marker of a true obstruction and a prognostic indicator of this pathology. In kidneys afflicted with a dilatated collecting system, a RI value ≥ 0.07- 0.75 implies a possible obstruction while lower values would appear to be associated with a non-obstructive dilatation (15, 30), A return to normal RI values after nephrostomy has been observed (15). Diagnostic accuracy of this procedure is adequate to distinguish between obstructive pyelectasia and the non-obstructive form and is estimated to be between 77% and 96% (17, 18, 30, 33).
Naturally, the length of time before identification of an obstruction using ECD will be determinant in predicting a return of RI to normal values. In general, if the obstruction is identified within the first 5 hours after the obstructive episode, a rapid return to normal values can be expected whereas if the obstruction occurred 18-24 hours before, it might take days or even weeks before RI returns to normal.

Conclusions

Traditional echo-tomography represents an excellent means of studying a patient with AKI. Advantages include its non-invasive nature and its speed of execution in revealing important morphological features of the renal parenchyma and the urinary tract. This advantage is useful for the nephrologist in assessing a new incoming patient and to determine important parameters such as prognosis and therapeutic options. The addition of ECD can also furnish important information concerning the functioning of the kidney and could be a determining factor in refining the elements of clinical suspicion present in the differential diagnosis.

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PRESENTATION

Echo-color-Doppler balance in dialysis patient.

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Summary

Ultrasonography is a non-invasive,well-controlled, quickly and easily available diagnostic procedure for the patient, is repeatable and not using ionizing radiation. For all these features plays an important role in the clinical management of patients undergoing dialysis. A census of the National Renal Ultrasound Study Group from Italian Society of Nephrology revealed that the 73.04% of Italian Departments of Nephrology and Dialysis are equipped with the ultrasound scanning and this one is commonly used in normal working routine.The main fields of application of this methodology in dialysis patient are:vascular pathology (damages due to systemic atherosclerosis,study and monitoring of arteriovenous fistula), muscle-tendon pathology (caused by hyperparathyroidism and amyloidosis), hyperparathyroidism (parathyroid assessment) and neoplastic disease.

KEY WORDS: *Echo-color-Doppler; B-mode analysis; Non-invasive diagnosis; Dialysis; Prevention.*

INTRODUCTION

Nephrology is the medical branch which deals with the diagnosis and treatment of kidney disease.In the study of these diseases, particularly in recent decades, we have increasingly made use of the contribution of the ultrasounds (B-mode) and echo-color-doppler. A census of the from the *National Renal Ultrasound Study* from *Italian Society of Nephrology* showed that 73.04% of *Nephrology and Dialysis Departments* in Italy are equipped with and utilize the transducer as a tool in the normal work routine (1). Ultrasound is a simple method that does not require special skills from the operator, does not require the use of ionizing radiation nor traditional contrast media. As non-invasive, it is very well tolerated by patients and is easily available even in departments of Hospitalization. It allows the acquisition of multiple information with dynamic and comparative studies. For all of these features is the preferred tool in first level diagnostic. Particulary, is useful in Nephrology to manage many kidney diseases: diagnostic of size and morphology of renal shadows allow the specialist to distinguish presumably acute kidney failure from chronic one. Apart from the traditional use of ultrasound (images in B-mode), the Echo-color-Doppler became a routine use in Nephrology. This method exploits the physical phenomenon of the Doppler effect, provides both qualitative (we evaluate the presence, the signal direction) that quantitative data: peak systolic velocity, average speed, end-diastolic velocity, the Resistance Index (RI).
With qualitative analysis you can, for exampe, recognize as vascular images not clearly identified as such or recognize if the flow within a vessel occurs in normal or reverse direction; with quantitative analysis, you can measure speed and flow in normal or pathological vessels. In patients that relate to our Clinics is now routine do, beside the renal ultrasound, doppler of renal arteries, which allows the identification of ischemic nephropathy.

CLINICAL CHARACTERISTICS OF THE UREMIC POPULATION

Ultrasonographic methods can have the greatest scope of applicability in population with end-stage renal failure undergoing dialysis.
The reasons for this phenomenon are easily understood if you review the clinical features of these patients. Over the last two decades we have witnessed a dialysis population ageing. Also due to improvements in health-care field and improvement of dialysis techniques increasingly biocompatible, the survival rate of patients who are getting older and suffer from severe comorbidity has improved. In European countries it is estimated that approximately 30% of these people are suffering from

diabetes mellitus and in this population the prevalence of cardiovascular events is high (congestive heart failure/coronary disease/heart disease/peripheral vascular diseases/cerebro-vascular events). It is also known that the cardiovascular risk in dialysis patient is exponential if compared with that of general population (2). Next to the traditional risk factors (e.g. age, cigarette smoking, hypertension, diabetes mellitus, dyslipidemia, obesity, physical inactivity) dialysis patients have additional "risk factors" (eg. oxidative stress and chronic inflammatory condition caused by dialysis replacement; protein malnutrition) which contribute to accelerate atherosclerosis.Patients undergoing dialysis have alterations caused by uremic condition; for example,abnormal bone metabolism due to secondary hyperparathyroidism, amyloidosis from accumulation of β-2 microglobulin predisposing to musculoskeletal disorders;the incidence of cancer in this patient group is also high.

Applications

As easily understood, ultrasonography and the Color-Doppler are simple-to-use tool to diagnose and monitor all pathological conditions related to uremia:

– ***Vascular pathology***
  Districts of interest: coronary vessels/carotid arteries/lower limbs arteries/aorta
– ***Musculoskeletal and soft tissue pathology***
  District of interest: tendons/synovial joints/soft tissues/bursae
– ***Neoplastic disease/acquired cystic disease***

Other fields of applicability:

– ***Evaluation for creation of vascular access/monitoring vascular access***
– ***Evaluation of the degree of parathyroid hypertrophy***

Vascular pathology

The vascular pathology, which in accelerated atherosclerosis has its crucial event, manifests itself in different organs and systems.It is characterized by the presence of disseminated vascular calcification affecting mainly the wall of the arteries.

Ultrasounds, although they cannot discriminate intima from media arterial disease (3), sometimes allows to recognize the "unstable" atherosclerotic plaques (hypoechoic-anechoic areas with high risk of embolization) and therefore at risk of ischemic evolution. The most frequently districts affected by vascular damage in uremic population are:

– *Coronary vessels*: explorable only with invasive methods.
– *Carotid vessels*: the arterial intima-media thickness of the common carotid predict the risk for stroke and also for myocardial infarction (4) The Echo-color-Doppler discriminates between atherosclerotic fibrous-lipoid plaques (hypo-echoic,hardly evaluated by B-mode tecnique but quantifiable with the color-Doppler) and calcific plaques (hyper-echoic, with posterior shadow cone and then detected by traditional ultrasound). The method employs linear probes (5-7.5 MHz) with longitudinal and transverse scans. The analysis involves common carotid (CC), internal carotid (IC) and external carotid (EC). The bulb of the internal carotid is the tract most frequently involved in the process of atherosclerosis. The use of Color-Doppler allows to detect possible "aliasing", a turbulent flow indicative of stenosis, allows to determine the amount of stenosis by sampling the vessel at the level of stenosis itself and measuring the systolic peak velocity and its relations between IC and CC. The method is highly sensitive and specific.
– *Aorta/abdominal vessels*: in uremic population finding an abdominal aortic aneurysm (AAA) is more frequent than in general population and evolution is often faster (5).
  The AAA is a complication of atherosclerosis,frequently asymptomatic. It is defined as a dilation of the vessel with increase in size more than 50% of the tract above.
  The Echo-color-doppler is the first choice to analyze abdominal arteries and aorta. This method shows an excellent specificity and sensitivity (99%); it is useful to both screening and follow-up of vascular abdominal diseases.More rarely large abdominal vessels may be affected by steno-obstructive pathology. Also the presence of abdominal aortic calcifications represents a predictive index of coronary calcifications (6).
  Calcifications of the large arteries are typically scattered, extended and circumferential; they may involve the ostium of collateral vessels and cause a stenosis (e.g. renal artery stenosis with ischemic nephropathy); rarely may cause stenosis or complete occlusion (Leriche's syndrome) (5).
– *Peripheral arteries of lower limbs*: similarly to carotid disease, vascular disease of the lower limbs, more or less widespread, can lead to ischemic peripheral issues. The complication is critical ischemia that can lead to amputation. The ultrasound scan allows not only to define the localization and extension of arterial stenosing disease (less frequently dilatative) but also to obtain information regarding the hemodynamic of the district in order to determine the severity of the lesion. The best approach to assess the importance of a stenosis is to calculate the PSV samplig the signal at the level of stenosis and PSV detecting the signal upstream of the stenosis; an increase of PSV at the level of stenosis greater than 100% highlights a stenosis greater than 50%. A reduction of systolic-diastolic velocity (with downstream flow reduction) documents a critical stenosis greater than 80%. The absence of doppler signal (pulsed, color and power) enables us to detect a complete arterial occlusion.

Osteo-articular and soft tissues pathology

Secondary hyperparathyroidism (which follows alterations of the metabolism of calcium and phosphorus) and amyloidosis (that follows the deposition of amyloid fibrils in various tissues of the musculoskeletal system) predispose to degenerative diseases of tendons, bursae and articular capsules (uremic osteo-arthropathy). The ultrasound scan once again allows us to study these problems;it takes high frequency linear probes (7.5-15 MHz) for their high resolving power and superficial focus.In secondary hyperparathyroidism we can have pathological conditions characterized by spontaneous tendon ruptures that are ordinarily unilateral, more rarely bilateral (7). The most fre-

quently affected tendon is the femoral quadriceps. The scan reveals a hypo-anechoic area representing the complete or partial anatomical break of the two flap of the tendon.Frequent calcifications of periarticular soft tissue (tendons and bursae) are also easily detectable by ultrasound. Amyloidosis, a complication of uremia, can configure pathognomonic syndromes:

– *Padded shoulder syndrome*, characterized by tendinosis (structural thickening) of rotator tendons' cuff; tenosynovitis (an anechoic portion surrounding the hyper-echoic profile of the tendon) and tendinosis of the long head of biceps tendon,inflammation of subacromial-deltoid bursa (8)
– *Carpal tunnel syndrome*: due to abnormal deposition of amyloid in the carpal tunnel that determines a median nerve compression. Ultrasonography may show tendon tenosynovitis of the flexor tendons of fingers or anechoic deposits in other structures of the carpal tunnel such as transverse carpal ligament, perineurium, basement of the carpal tunnel.
– *Tenosynovitis of flexor and extensor tendons of fingers*: tendons are thickened and inhomogneous with extravasation of fluids at the level of tendon sheath, appearing stretched and hypo-echoic.
– *Baker's cyst*: a benign swelling of the semimembranous bursa found behind the knee joint.
The synovial sac of the knee joint can, under certain circumstances, produce a posterior bulge, into the popliteal space, the space behind the knee. When this bulge becomes large enough, it becomes palpable and cystic. Most Baker's cysts maintain this direct communication with the synovial cavity of the knee, but sometimes, the new cyst pinches off.

Neoplastic disease/acquired cystic kidney disease /silent kidney

The ultrasound follow-up in dialysis patients is crucial because the condition of uremia predisposes to the incidence of tumors (9). The risk of developing cancer is greater in young dialysis patients and decrease gradually with age; the most frequent cancers are those involving kidney, bladder and thyroid (10). In uremic patients, thanks to a better surveillance, you can diagnose cancer at early stages and this lead to a its complete eradication. A typical finding in dialysis patients is "silent kidney" (renal shadows significantly reduced in size) with thinning of renal cortex and little or none differentiation of renal medulla, but we can also have an acquired cystic pathology. In this case, renal morphology is progressively subverted by the appearance of multiple cysts, usually small, most frequently localized in the renal cortex. These cysts rarely cause an enlargement of the organ and can lead to renal cancer. Simple cysts appear as usual: at ultrasound visualization, have liquid content and the characteristic reinforcement of the posterior wall.
Renal cancer, more easily recognized if the solid mass is projected outside the surface of a atrophic kidney, is hardly diagnosed in kidneys with cystic acquired disease. If the cysts show something complicated, the B-mode image should be integrated with the color-Doppler technique to search any vessel allowing differential diagnosis: hemorrhagic cyst versus cancer.

Creating and monitoring vascular access

The success of a vascular access in uremic population is a prerequisite for an adequate dialysis. The radio-cephalic arterious-venous fistula represents the gold standard vascular access for dialysis patient. Pre-dialysis timing is important to define the possibility to create a functioning fistula. Thanks to the echo-color-Doppler study we can determine the caliber of arteries and veins of the forearm and arm and we are able to predict the success of vascular access (11, 12). In this population of patients, the integrity of arteries of upper limbs is often compromised by age, by the coexistence of diabetes mellitus or atherosclerosis. Instead, the venous vessel may have been compromised by frequent venipuncture rather than by antineoplastic agents in patients with cancer. Once created, the vascular access can face many complications, among these the most popular are the partial or total thrombosis and stenosis. Even in these cases, the ECD is an indispensable tool that allows the assessment of the extension of thrombotic process, the onset, the position and the extent of stenosis usually localized at the proximal efferent venous tract. When the vascular access cannot be created, it's necessary to position a central venous catheter in femoral vein or internal jugular vein. For a safe procedure, we can perform the maneuver under ultrasound guidance.

Assessment of the degree of parathyroid hypertrophy

In the early stages of chronic nephropathy the renal osteodystrophy can be also found, resulting to reduced endocrine production of vitamin D by the kidneys. This deficiency affects a compensatory response of parathyroid glands causing a marked hypertrophy. Medical treatment of this condition relies on administration of vitamin D analogues, use of phosphorus binders and calcimimetic drugs. If the hyperparathyroidism is refractory to medical treatment, total or subtotal parathyroidectomy may be needed (13). Monitoring with ultrasound the volume of parathyroid glands in all hyperparathyroidism stages is therefore useful; this volume would seem to correlate with the severity of the renal disease. The parathyroid gland becomes detectable when it becomes hyperplastic (increase in size, > 5 mm of diameter) and acquires the solid homogeneous structure of a nodule. The gland shape is typically oval, sometimes round, the structure is widely hypo-echoic sometimes with calcifications; the capsule looks like a hyper-echoic border an the ECD shows intraparenchymal vessels.

Conclusions

Ultrasounds,with their multiple applications, represent a tool that has become indispensable in the daily work of all Nephrologists in all stages of kidney disease (even more in patients on dialysis).

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Echoguided treatment of simple renal cysts: Our experience from 1995 to 2010.

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Summary

The simple renal cysts are the most frequent lesions of kidney in adults. Approximately 30% of subjects older than 70 years presents a simple renal cysts. It is well accepted that a simple renal cyst without symptoms does not require any treatment.
Objective: Evaluate the efficacy of the echoguided treatment of simple renal cysts with a single sclerotherapy.
Material and Methods: Since 1995 to March 2010 in our clinic 329 patients underwent percutaneous drainages of simple renal cysts. In 56 cases (17% of patients) it was a simple aspiration, in 69 cases (21%) a drainage was placed for 24 hour continuous draining and in 204 cases (62%) lesions were treated by sclerotherapy. After aspiration of fluid we injected inside the cyst 99% ethanol in the amount equal to 30% of aspirated volume and never exceeding 60 ml. After 40 minutes we aspirated ethanol and removed the drainage.
Results: The outcome was considered good if the size of the cyst was less of 50% of the primary size. Percutaneous drainage with sclerotherapy showed a success rate of almost 100% using 99% ethanol. However, this method is not completely free from complications.
Conclusions: The long-term results and the mini-invasive modality of treatment without hospedalization are the most important advantages of this procedure. Furthermore our experience showed a good success rate with a single sclerotherapy with benefit to the patient and lower costs of procedure.

KEY WORDS: Simple renal cysts; Sclerotherapy; Percutaneous drainage; Mini-invasive treatment.

INTRODUCTION

Simple renal cyst is a non-neoplastic disease of renal parenchyma. They are quite common in adults, with an incidence of at least 20% at age 40 years and 33% at age 60 years (1). Currently is not clear etiopathogenic origin of this desease, that can be caused by congenital or acquired disorders.
They are characterized by a thin wall and inside the wall there is a clear liquid, amber in appearance, even if this, macroscopic appearance is called "blue-domed". Calcifications can be inside. In approximately 5% of simple renal cysts the content can be liquid blood and in half of these cases may be associated with a tumor inside (13-15).
In most cases, simple renal cysts are asymptomatic. In other circumstances the cyst may grow up causing compression phenomena responsible for tensive pain in the side. In other cases it may become infected or bleed and can be associated with more severe symptoms. Rare are the cases of hypertension or renal dysfunction related to compression of the renal and urinary tract, respectively.
The diagnosis is occasional in most cases, during ultrasound screening of the abdomen performed for other reasons (2). Laboratory tests show no deterioration of renal function and examination of the urine is often normal. The CT-scan, however, becomes useful in the suspected presence of a tumor or if it needs more detailed study of the relationship that the cyst contracts with neighboring structures.
It is well accepted that a simple renal cyst without symptoms does not require any treatment (2-4).
The main indications for treatment are:
- Symptoms of mass effect
- Compression of the urinary tract

- Hypertension
- Assessment of cytological
- Size greater than or equal to 9 cm
- "Anxiety of the patient"

The procedure is contraindicated in the following circumstances:
- Haemorrhagic diathesis
- Severe respiratory insufficiency
- Severe obesity
- Malformations

Management of a symptomatic renal cyst can be accomplished with several methods: percutaneous aspiration with or without instillation of sclerosingagents, percutaneous marsupialisation, open cyst unroofing and, as the most recently reported method, laparoscopic or retroperitoneoscopic cyst unroofing (5-10).

Material and methods

The ultrasound guided percoutaneous treatment is now a safe technique and a valid alternative to open surgery or laparoscopy. The technique is performed under local anesthesia and may be a simple puncture, puncture and drainage or puncture and sclerotherapy. Evacuative simple puncture is used especially when liquid inside the cyst is blood or corpuscoleted liquid. It is a diagnostic puncture, with a risk of recurrence of 30-80% depending on the case.
Treatment with percutaneous drainage consist in the positioning in the cavity of the cyst, after complete aspiration of all fluid inside, of a "nephrostomy drainage" for 24 hours. The aim of this technique is to cause a collapse of the cyst's walls. In this case the risk of recurrence is 65-80%.
Surgical access can be posterior or posterolateral . In the first case the patient is supine and the puncture is performed below the 12th rib, about 10 cm away from vertebral spinous process. This access is safe but also not confortable for patient. In the second case patient is in prone-oblique position and the puncture is performed on the midaxillary line. This access is more comfortable for the patient but has an increased risk of intestinal perforation.
Since 1995 to March 2010 in our clinic 329 patients underwent percutaneous drainages of simple renal cysts. In 84% of cases we found individual cysts with sizes from 84 mm to 191 mm. We found lower polar cysts in 47% of cases, upper polar cysts in 37%, cysts in the middle of kidney in14%, and cysts near renal pelvis in 2%. In 56 cases (17% of patients) it was simple aspirations, in 69 cases (21%) a drainage was placed for continuous 24 hours, 204 (62%) lesions were treated by sclerotherapy. Sclerotherapy was performed with 99% ethanol in 94% of cases and with fibrin glue (tissucol) in the remaining 6%.
After aspiration of fluid inside the cyst, we fix the nephrostomy catheter to the skin. The fluid aspirated from the cyst cavity was sent to the laboratory for cytologic and microbiological examination. Then the cystic cavity is filled with saline solution that is immediately aspirated with syringe. After that we inject 99% ethanol in the amount equal to 30% volume aspirated and never exceeds 60 ml. We ask the patient to change often his positions. After 40 minutes we aspirate ethanol and remove drainage. Patients are then discharged.

Results

The outcome was considered good if the size of the cyst was 0% or less of 50% of the primary size. Percutaneous drainage with sclerotherapy showed a success rate of almost 100% using 99% ethanol. In patients treated with aspiration alone or with placement of percutaneous drainage we observed a complete relapse rate of 85% and 39% respectively. Table 1 shows our results.
However, this method is not completely free from complications, such as the burning pain (29%), vagal syndrome (11%) intracystic hemorrhage (0.5%).

Discussion

Over the years different authors have used different options about this procedure. The biggest difference is

Table 1.

	Simples aspiration	Percutaneous drainage	Sclerotherapy with tissucol	Sclerotherapy with alcol etilico 99%
Succes rate	0%	14%	17%	~ 68%
Relapse < 50% of the volume	6%	22%	3%	~ 32%
Recidiva > 50 del volume	9%	25%	30%	0%
Complete relapse	85%	39%	50%	0%

Table 2.

Author	Year	Patients	Treatment	Success (complete/partial)	Volume Reduction	Disappearance of symptoms
Porpiglia	1996	49	Repeated sclerotherapy	96% - /	/	/
Fontana	1999	69	Repeated sclerotherapy	98% - /	/	55%
Paananen	2001	32	Repeated sclerotherapy	22% - /	79%	75%
Delakas	2001	68	Repeated sclerotherapy	83%-11%	/	/
Akinci	2005	97	Single sclerotherapy	18% - /	93%	83%

related to the number of treatments to be carried out. Various substances acting like sclerosing agent were used (phenol, lipiodol, alabrina, quinocrina, methotrexate, 98% ethanol, tetracycline, fibrin glue, etc.). Ethanol 99%, is one of the best the because contact between drug and cells of the cyst wall is able to determine the death of the latter within 1-3 minutes. Are needed 4-12 hours to have the penetration of the capsule. For example *Porpiglia et al.* reported that 98% of simple renal cysts disappeared after percutaneous drainage and three alcohol sclerotherapies at intervals of 24 hours (5). For *Paananen et al.* the outcome was satisfactory in 87% of the patients with a simple renal cyst and treated with a single 99% ethanol infusion (11). Table 2 shows the different results for different techniques of sclerotherapy.

Conclusions

Percutaneuos echoguided treatment of simple renal cysts with sclerotherapy is not completely free from complications, such as the burning pain, vagal syndrome, intracystic hemorrhage. Our experience shows this treatment is a valid alternative to open surgery or laparoscopy. The long-term results, the mini-invasive treatment without hospedalization are the most important advantages of this procedure.Furthermore our experience shows that you can get a good success rate with a single sclerotherapy with benefit to the patient and lower costs of procedure.

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PRESENTATION

Hydrocele with surprise. Case report and rewiew of literature.

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Summary

Introduction: *Hydrocele is a fluid collection between tunica vaginalis and testis. Approximately 10% of testicular cancers occurs with a reactive hydrocele.*
Case report: *A 64 year old male presented with a 30 year history of left hydrocele, progressively increasing. Physical examination demonstrated a left large hydrocele, transilluminable, not under pressure. Ultrasonography showed a "corpusculated hydrocele with vaginal hypertrophy jutting out near the head of the epididymis, perhaps caused by an inflammatory reaction […]" As the patient showed only a minimal discomfort due to the groin swelling, without pain, surgical excision was planned without priority (Class C < 180 days).*
Results: *The surgical exploration showed a paratesticular papillary neoplasm of 3 cm. Intraoperative pathologic examination of a frozen sample demonstrated a "borderline papillary cystadenoma". The Left orchifunicolectomy was performed. The definitive histological examination showed a "left paratesticular Papillary Serous Tumor of Low Malignant Potential (PSTLMP) with morfoimmunoistochemical features of Mullerian origin of neoplasm". Computed tomography (CT) was negative for lymph nodes and metastasis. In agreement with the oncologist we decide for atchful waiting.*
Discussion: *Despite of rich personal experience of resections and eversions of the vaginal tunic, an urologist rarely observes a case of paratesticular cancer. A PubMed search found 28 citations between 1985 and 2010 with 42 reported cases of paratesticolar neoplasm, including 27 with malignancy features. Rhabdomyosarcoma is the most common, followed by mesothelioma, adenocarcinoma and neuroblastoma. This case report consists of a "borderline" neoplasm for which in the literature, after orchiectomy, it is reported no case of recurrence or metastasis (with a follow up of up to 18 years).*
Conclusion: *The banality of the disease never must underestimate the possibility of an undetected cancer.*

KEY WORDS: *Paratesticular tumor; Borderline tumor; Mullerian neoplasm; Hydrocele.*

INTRODUCTION

The hydrocele is a fluid collection between tunica vaginalis and testis. The diagnosis is performed by scrotum transillumination. Since approximately 10% of testicular cancer occurs with a reactive hydrocele, when you have doubts it is useful to confirm the diagnosis with an ultrasunography (1).

CASE REPORT

Male, 64 years. Refers an history of left hydrocele from at least 30 years, progressively increasing. Objective exam: left large hydrocele, transilluminable, not under pressure. He showed a recent scrotal ultrasonography which reported: "Corpusculated hydrocele with vaginal hypertrophy, jutting out near the head of the epididymis (Figure 1), perhaps caused by an inflammatory reaction (Figure 2), however it require subsequent controls and a possible confirmation during the exploration for the hydrocele surgical correction". No other ultrasonograhy to compare were performed before. As the patient showed only a minimal discomfort due to the groin swelling, but not pain, he was booked in the waiting list to be undergoing to the eversion

Figure 1.
Ultrasonography which reported: "Corpusculated hydrocele with vaginal hypertrophy, jutting out near the head of the epididymis…".

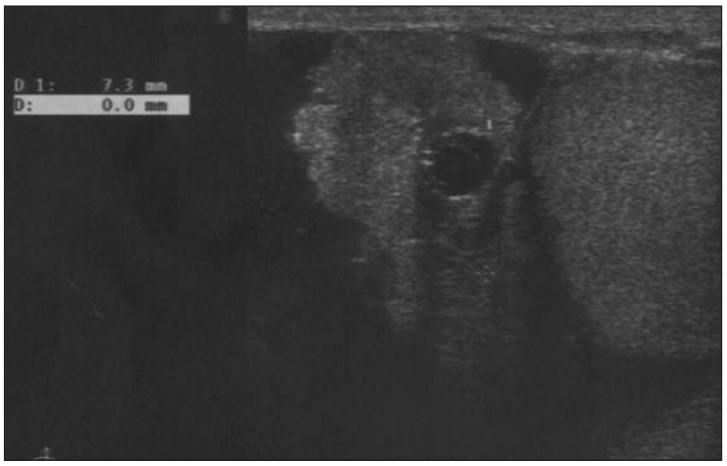


Figure 2.
Ultrasonography: "… perhaps caused by an inflammatory reaction…".

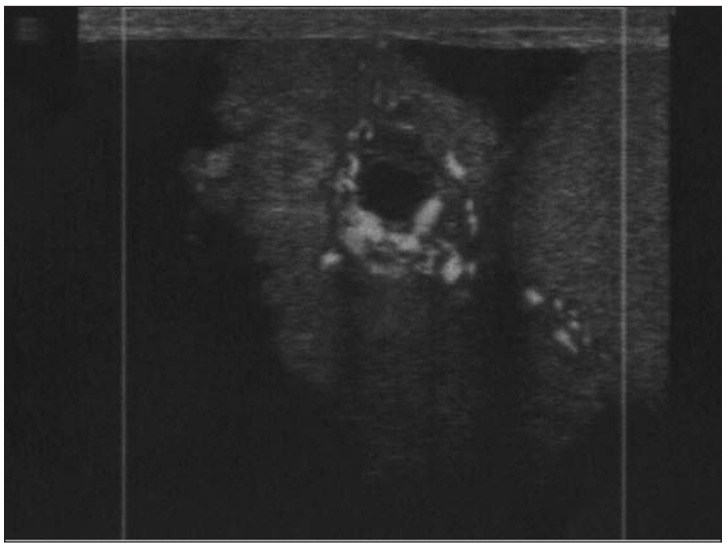
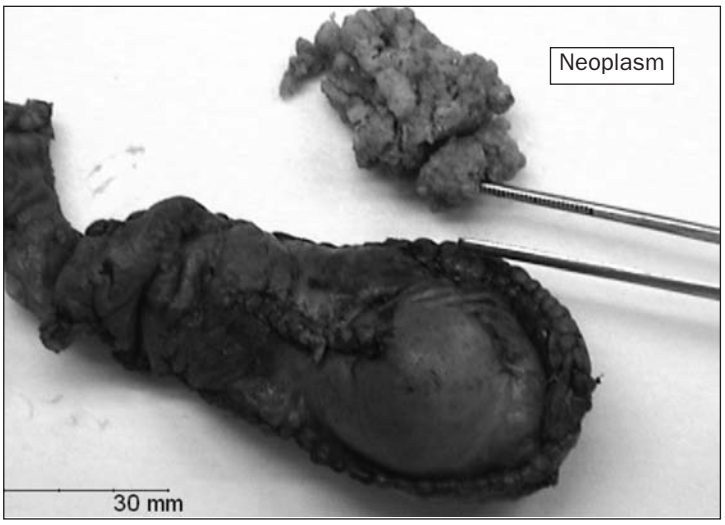


Figure 3.
Grossly, the tumor appears as a papillary solid mass, greysh, size 4 x 2 cm, no necrotic areas.



and resection of left vaginal tunic with Priority Class C (< 180 days) (2).

Results

After about 5 months the patient was taken to the operating room after signing the informed consent for resection and eversion of the left vaginal tunic. When the vaginal tunic was opened, after the aspiration of yellow liquid like lemon juice, between the upper pole of the testis and the epididymis head there was a paratesticular papillary neoplasm of 3 cm. The intraoperative consultation (after cryosection) described a "borderline papillary cystadenoma". Since the patient was awake and oriented (in spinal anesthesia) the informed consent to the left orchifunicolectomy could be obtained in the course of operation.
Grossly, the tumor appears as a papillary solid mass, greysh, size 4 x 2 cm, no necrotic areas (Figure 3).
Microscopic sections revealed well-formed papillae with fibro-vascular core lined by serous cuboidal or columnar epithelial cells, often in many layers, with apical cilia (Figure 4). The epithelium was bland, mitotic figures were present, but rare, no microinvasion and no flank nuclear anaplasia were identificated (Figure 5).
Psammona bodies were not observed. Tumour wasn't associated with teratomatous elements of testis. Epithelial cells displaied immunoreactivity identical to borderline papillary serous tumors of ovary: strong and diffuse positive staining with broad-spectrum Cytokeratins AE1/AE3, Cytokeratin 7, EMA, CA125, WT1, Estrogen Receptor/1D5, Progesteron receptor/ PgR636 and Vimentin; negative staining with CEA, Cytokeratin 20, Cytokeratin 5/6, Calretinin, CD15 and PLAP. Proliferative activity by MIB1 staining was 5%.
Definitive histological examination: Left Paratesticolar Non Invasive Borderline serous papillary tumor (Papillary Serous Tumor of Low Malignant Potential or PSTLMP) with morfoimmunoistochemical of Mullerian neoplasm". He performed CT: negative for lymph nodes and metastasis. In agreement with the oncologist we decide for the watchfull waiting.

Discussion

The urologists used to treat hydrocele from the early days of postgraduate course. Despite the rich personal experience of resections and eversions of the vaginal tunic, each urologist rarely met any single case of paratesticular cancer. The *PubMed* search found 28 citations between 1985 and 2010 with 42 reported cases of paratesticular neoplasm, including 27 cases with malignancy features (Table 1).
Rhabdomyosarcoma is the most common, followed by mesothelioma, adenocarcinoma and neuroblastoma (3).

Figure 4.
Microscopic sections revealed well-formed papillae with fibro-vascular core lined by serous cuboidal or columnar epithelial cells.

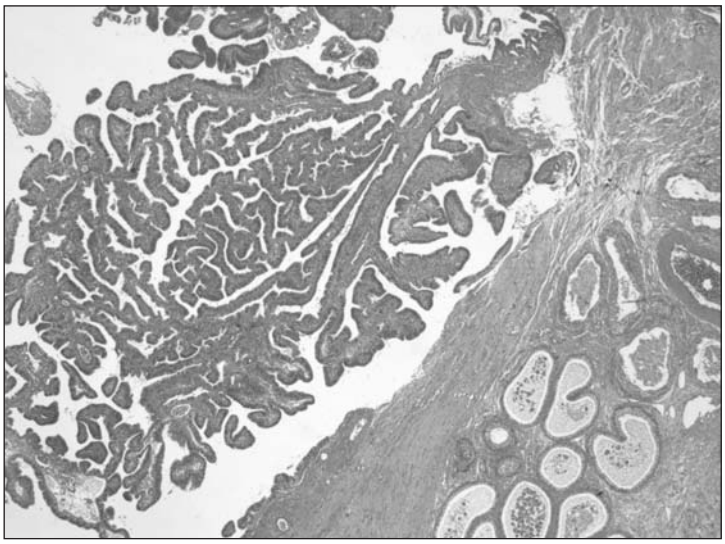
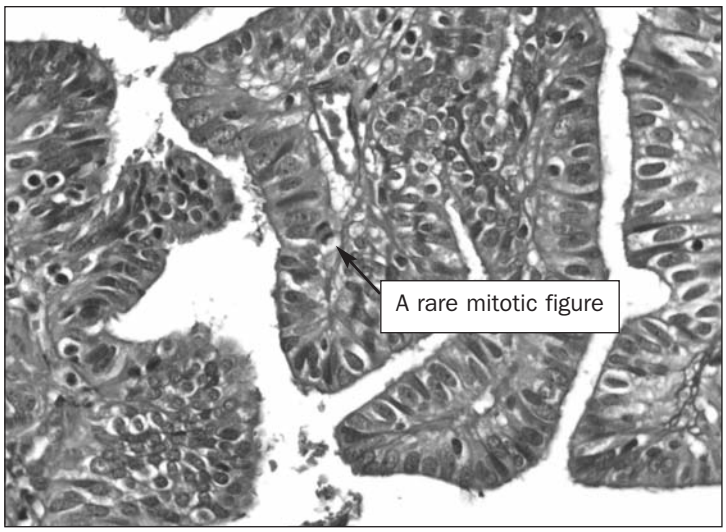


Figure 5.
mitotic figures were present, but rare, no microinvasion and no flank nuclear anaplasia were identificated.



The case report consists of a "serous borderline" tumor of paratestis for which in the literature, after performing the orchiectomy, it is reported no case of recurrence or metastasis (with a follow up of up to 18 years) (4).
Papillary Serous Tumor of Low Malignant Potential (PSTLMP) may occur in the tunica vaginalis, testis, spermatic cord and epididymis. It is grossly, microscopically and immunoistochemically identical to ovarian serous borderline tumor. It is usually unilateral. Patients range in age from 6 to 77 years (mean 56 years). Proliferative activity by MIB1 staining ranges from 1% to 10% (mean 5.5%). Its histogenesis is under discussion. Since this tumor is similar to that seen in the female genital tract and specially in the ovary, this tumor belongs to the group of Mullerian Epithelial Tumor or Ovarian-Type Epithelial Tumor (OTET).
The differential diagnosis include papillary serous carcinoma (tipically consisted of invasive papillae), papillary cystoadenoma of epididymis (benign neoplasm that arises from the efferent duct epithelium; often is bilateral and associated with von Hippel-lindau syndrome) and benign and malignant papillary mesothelioma (asbestos exposure correlated neoplasm with a biphasic histologic pattern and positive staining for Calretinin and CK 5/6).
Its histogenesis is under discussion. Early in development, tissue have the potential to develop into either male or female structure. Bilateral urogenital ridges grow from coelomic epithelium around week 5 of development. If no signals occur to transform the structure into testis, the organ develops into an ovary.
The same coelomic epithelium is responsible for both male and female structure; therefore, a tumor affecting this tissue could affect either sex. Epithelial tumors of testis that resemble ovarian tumors may be seen in either testis and paratestis. Testicular disease is less common than paratesticular disease, and the etiology is

Table 1.
From 1985 to 2010: 28 citations with 42 reported cases of paratesticular neoplasm (3).

Malignant tumors	**Cases**	**Benign tumors**	**Cases**
- epithelial origin	1	- leiomyoma	4
- various	6	- fibroma	2
- vaginal mesothelioma	3	- fibroma	2
- clear cells adenocarcinoma	3	- cystoadenoma	9
- rhabdomyosarcoma	8		
- thecoma	1		
- liposarcoma	1		
- lymphoma	1		
- neuroblastoma	3		
Total	**27**	**Total**	**15**

unknown. It has benn hypothesized that these lesions maight development from the remnants of the Mullerian duct (for example from appendix testis, a vestigial remnant of the male Mullerian duct) or from mesothelial inclusions of the tunica vaginalis by the process of mullerian neometaplasia. Intratesticular tumors are hypothesized to result from areas of coelomic epithelium that became trapped within the testicular tissue.
An additional theory, although less popular, is that the tumor develops in the ovarian component of a hermaphrodite (5).

Conclusions

The banality of a disease like hydrocele never must underestimate the possibility of an undetected cancer.

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PRESENTATION

Semen quality and hormonal levels in infertile patients with varicocele.

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Summary

Objective: *Aim of this study was to evaluate the semen quality and the serum concentration of follicle-stimulating hormone (FSH) and Testosterone (T) in infertile patients with and without varicocele.*

Material and Methods: *365 infertile patients undergoing Assisted Reproduction Tecnique (ART) were retrospectively included in the study. All subject were evaluated by history, physical examination, semen analysis, semen culture, mixed anti-immunoglobulin reaction test (MAR) for demonstration of sperm agglutination antibodies IgG and IgA, serum FSH and T determination.*

Results: *We observed 97 (26.6%) patients affected by varicocele compared to 268 (73.4%) without varicocele. A significant reduced percentage of motile spermatozoa (24.58 ± 21.68 vs 21.01 ± 12.62, p < 0,001) and lower sperm concentration (15.50 ± 23.30 vs 16.50 ± 15.22, p < 0.001) were observed in patients with varicocele compared to patients without varicocele. No significant differences were observed in sperm vitality between the two population of men with and without varicocele. Serum FSH (10.42 ± 10.84 vs 9.11 ± 18.81, p < 0.001) and Testosterone (5.73 ± 5.97 vs 5.21 ± 2.43, p < 0.001) levels were significantly higher in patients with varicocele compared to patients without varicocele. Detection of IgG and IgA sperm antibodies were negative in both man with and without varicocele.*

Conclusion: *The direct connection between varicocele and infertility is not clear. The data of the present study suggest that the presence of a clinical varicocele rule out fertility in men affecting the hypothalamic pituitary-gonadal axis.*

KEY WORDS: *Varicocele, Infertility, Semen quality, FSH, Testosterone.*

INTRODUCTION

Varicocele is a vascular lesion characterized by abnormal tortuosity and dilatation of the veins of the pampiniform plexus involving both the internal spermatic and cremasteric veins (1). The prevalence of varicocele in the general population is estimated to be 15%, although the prevalence of varicocele amongst infertile men ranges from 30 to 40% (2). The mechanism by which varicocele causes variable effect on male fertility is still unknown. The aetiology may be multifactorial and may include a pre-existing genetic disposition, but there are other factors involved like hyperthermia, testicular blood flow and venous pressure changes, reflux of renal/adrenal products, hormonal dysfunction, autoimmunity, defects in acrosome reaction and oxidative stress (3). Several studies highlighted that varicocele can determine changes in semen parameters leading to infertility. MacLeod first described the seminal profile in infertile men with varicocele and observed an abnormal seminal pattern with oligozoospermia, asthenozoospermia and a teratozoospermia characterized by an increase of immature germinal cells, especially early spermatids. The Author defined a "stress pattern" as pathognomonic of varicocele (4). *Pasqualotto et al.* observed that infertile patients with varicocele have higher levels of FSH, smaller testes, lower sperm concentration and motility compared with controls with or without varicoceles (5). *Vivas-Acevedo et al.* suggested that both the varicocele grade and an increase of age in men with varicocele

could determine the extent of alteration to semen quality (6). The purpose of this study was to evaluate the sperm parameters, and the serum concentration of follicle-stimulating hormone (FSH) and Testosterone (T) in infertile patients with and without varicocele.

Materials and Methods

365 patients undergoing ART at *University Hospital of Bari*, from January 2006 to August 2010, were retrospectively evaluated. Inclusion criteria were unexplained infertility, defined as a failure to establish a pregnancy within one year with unprotected intercourse, and/or oligoasthenospermia, excluding patients with positive semen colture for pathogenic bacterial species (Gram-negative and positive), *Ureaplasma urealyticum*, *Chlamydia trachomatis* and viral infection (HIV, HBV, HCV, CMV), female partner with endometriosis, tubal factor and ovarian disorders.

All subjects were evaluated by history, physical examination, semen analysis, semen culture, serum hormonal determinations of FSH and T. Varicocele was diagnosed by physical examination through palpation of the spermatic cord before and during a Valsalva maneuver with the patient in a standing position. The diagnosis was confermed by Doppler ultrasonography and based upon the clinician's subjective impression of either venous dilatation or reflux of blood. Varicocele was defined by Doppler ultrasound with *Sarteschi's classification*: grade 1, prolonged reflux, detectable at the scrotal emergency only with functional maneuvers; grade 2, sopratesticular reflux only with functional maneuvers; grade 3, peritesticular evident reflux from the functional operations; grade 4, already evident reflux in basic condition and upgradeable with functional maneuvers; grade 5, already evident reflux in basic condition, but not significant upgradeable with functional maneuvers (7). Semen samples were collected after 3-5 days of sexual abstinence in sterile containers and analyzed according to *World Health Organization guidelines* (WHO) (8). All seminal samples were tested by the *SpermMAR™ (Origio)* kit for IgA and IgG detection of sperm antibodies. Statistical analysis was performed with t-Student test using *MedCalc software* (version 11.3.8.0). $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the demographic data of the patients evaluated. Patients with grade 1 varicocele were considered normal. 97 (26.6%) infertile patients were affected by varicocele compared to 268 (73.4%) infertile patients without varicocele.

The distributions of semen parameters and hormone levels are presented in Table 2. A reduced percentage of motile spermatozoa (24.58 ± 21.68 vs 21.01 ± 12.62, $p < 0,001$) and a significant lower sperm concentration (15.50 ± 23.30 vs 16.50 ± 15.22, $p < 0.001$) were observed in patients with varicocele compared to patients without varicocele. No significant differences were observed in sperm vitality between the two population of men with and without varicocele. We observed an abnormal sperm quality in 86 (88.6%) patients with varicocele and 233 (86.9%) patients without varicocele. Serum FSH (10.42 ± 10.84 vs 9.11 ± 18.81, $p < 0.001$) and testosterone (5.73 ± 5.97 vs 5,21 ± 2,43, $p < 0.001$) levels were significantly higher in patients with varicocele compared to patients without varicocele. Detection of IgG and IgA sperm antibodies were negative in both groups of patients with and without varicocele.

Discussion

The results of this study, according to previous reports, have documentated a reduced semen parameters in men with varicocele compared with patients without varicocele (9). Seminal abnormalities might be due to a gradual temporal loss of normal spermatogenesis as a result of higher intratesticular temperature and subsequent cell injury or loss (6, 10). In 1993 *Gorelick* and *Goldstein* demonstrated that varicocele is found in 35% patients with primary infertility and in 81% of patients with secondary infertility, implying that secondary infertility is caused by declining of semen parameters related to the long-term deleterious effect of an uncorrected varicocele (11). These data suggested that the presence of varicocele for over time causes a diminution in sperm quality. Moreover the findings of elevated serum FSH concentration in infertile patients with varicocele has led to the lower sperm concentration and sperm motility (6). In the present study we report a higher value of FSH and Testosterone levels in patients with varicocele comparing to patients without varicocele. In particular, elevated testosterone could be due to a testicular compensatory mechanism related to androgen receptor down-regulation or suppressed tonus of the internal spermatic vein (12).

Conclusion

In conclusion patients with varicocele compared to patients without varicocele have significantly lower sperm concentration, decreased sperm vitality and motil-

Table 1.
Demographic data.

	Varicocele (n = 97; 26.6%)	No varicocele (n = 268; 73.4%)
Age	37.61 ± 5.60	36.93 ± 5.53
Varicocele II grade	53 (54.6%)	
Varicocele III-V grade	44 (45.4%)	

Table 2.
Semen parameters and hormone levels.

	Varicocele (n = 97)	No varicocele (n = 268)	P value
Testosterone (ng/ml)	5.73 ± 5.97	5,21 ± 2,43	p < 0.001
FSH (UI/ml)	10.42 ± 10.84	9.11 ± 18.81	p < 0.001
Semen Volume (ml)	3,48 ± 1.95	2.55 ± 0.96	p < 0.001
Sperm Concentration (mil/ml)	15.50 ± 23.30	16.50 ± 15.22	p < 0.001
Motility (%)	24.58 ± 21.68	21.01 ± 12.62	p < 0,001
Normal Morphology (%)	26.69 ± 14.19	28.08 ± 11.96	0,046
Vitality (%)	54.13 ± 28.14	58.00 ± 26.06	0,369 (n.s)
Normal Spermiogram	11 (11,4%)	35 (13,1%)	
Pazienti con MAR test IgG e IgA (< 10% attached particles)	97	268	

ity and abnormal sperm morphology, and in addition they showed a higher level of FSH and T. Our data suggest that the presence of a clinical varicocele does rule out fertility in men affecting the hypothalamic pituitary-gonadal axis. Further studies on autoimmunity, defects on acrosome reaction and oxidative stress have to be made to clarify this issue and to identified molecular markers of damaging effects of varicocele on spermatogenesis.

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